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(57) Abstract

The present invention is directed to a pharmaceutical composition including a hydrophobic therapeutic agent having at least one ionizable functional group, and a carrier. The carrier includes an ionizing agent capable of ionizing the functional group, a surfactant, and optionally solubilizers, triglycerides, and neutralizing agents. The invention further relates to a method of preparing such compositions by providing a composition of an ionizable hydrophobic therapeutic agent, an ionizing agent, and a surfactant, and neutralizing a portion of the ionizing agent with a neutralizing agent. The compositions of the invention are particularly suitable for use in oral dosage forms.

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COMPOSITIONS AND METHODS FOR IMPROVED DELIVERY OF IONIZABLE HYDROPHOBIC THERAPEUTIC AGENTS

FIELD OF THE INVENTION

The present invention relates to drug delivery systems, and in particular to pharmaceutical compositions for the improved delivery of ionizable hydrophobic compounds and methods therefor.

BACKGROUND

Hydrophobic therapeutic agents, *i.e.*, therapeutic compounds having poor solubility in aqueous solution, present difficult problems in formulating such compounds for effective administration to patients. A well-designed formulation must, at a minimum, be capable of presenting a therapeutically effective amount of the hydrophobic compound to the desired absorption site, in an absorbable form. Even this minimal functionality is difficult to achieve when delivery of the hydrophobic therapeutic agent requires interaction with aqueous physiological environments, such as gastric fluids and intestinal fluids. Pharmaceutical compositions for delivery of such hydrophobic therapeutic agents must carry the hydrophobic compound through the aqueous environment, while maintaining the hydrophobic compound in an absorbable form, and avoiding the use of physiologically harmful solvents or excipients.

A number of approaches to formulating hydrophobic therapeutic agents for oral or parenteral delivery are known. Such approaches include, for example, formulations in which the hydrophobic therapeutic agent is present in an oil-in-water emulsion, a microemulsion, or a solution of micelles, liposomes, or other multi-lamellar carrier particles. While such approaches may be appropriate for some ionizable as well as non-ionizable hydrophobic therapeutic agents, they fail to take advantage of the unique acid-base chemical properties, and associated solubility properties, of ionizable compounds.

In particular, unlike non-ionizable hydrophobic therapeutic agents, ionizable hydrophobic therapeutic agents can be rendered soluble in aqueous solution if the pH of the solution is adjusted to ionize the therapeutic agent. Such an approach is well known in the art. For example, U.S. Patent No. 5,773,029 is directed to a pharmaceutical composition of an acidic drug, wherein the solubility of the acidic drug is enhanced by simultaneous salt formation with an organic or inorganic base and complexation with a

cyclodextrin. The resultant drug/cyclodextrin/base complexes reportedly are readily soluble in water in high concentrations.

U.S. Patent No. 5,360,615 discloses a pharmaceutical carrier system for an acidic, basic or amphoteric pharmaceutical agent in which the pharmaceutical agent is partially ionized by an acid or base in a polyethylene glycol-based solvent system. The pharmaceutical agent reportedly shows enhanced solubility in the partially ionized form. The reference also discloses that addition of glycerin, propylene glycol and/or polyvinylpyrrolidone further enhances the solubility of the pharmaceutical agent in the polyethylene glycol base. However, the invention is limited to polyethylene glycol-based solvent systems and a narrow range of ionizing agent concentration, and there is no disclosure of other solvent systems. Thus, its utility is severely limited.

Similarly, U.S. Patent No. 5,376,688 discloses a pharmaceutical solution of an acidic, basic or amphoteric pharmaceutical agent. The solution includes a pharmaceutical agent, an ionizing species, and a solvent system. The solvent system can be diethylene glycol monoethyl ether, glycerol caprylate/caprate, polyglycerol oleate, alpha-hydro-w-hydroxypoly(oxyethylene)-poly(oxypropylene)-poly(oxyethylene) block copolymers, or mixtures of those components. The solvent system can also be a mixture of polyethylene glycol and a polyoxyethylene sorbitan ester. Optional components include water, glycerin, propylene glycol, and polyvinylpyrrolidone. However, the invention is limited to these particular compounds and a narrow range of ionizing agent concentration, rendering its utility severely limited. Moreover, some of the solvent system components show poor or questionable biocompatibility, and thus would be impractical for drug delivery to a patient.

A further problem with conventional approaches to solubilizing ionizable hydrophobic therapeutic agents is the difficulty in maintaining the solubilized therapeutic agent in solubilized form. Thus, for example, while ionizing an acidic therapeutic agent with a base may increase its solubility, the therapeutic agent is prone to precipitation in the gastrointestinal tract due to the acidic pH conditions encountered upon administration to a patient, and the approximately 10 to 100-fold dilution expected in gastrointestinal or intestinal fluids. This precipitation is particularly disadvantageous, since the precipitated therapeutic agent is essentially unavailable for absorption, leading to difficulties in controlling dosages, and a need to administer large doses of the therapeutic agent to ensure that a therapeutically effective amount reaches the absorption site in a

bioavailable form. Such difficulties necessarily result in increased costs, and compromised patient safety and therapeutic effectiveness.

Thus, there is a need for versatile and effective pharmaceutical compositions that overcome these deficiencies in the prior art.

SUMMARY OF THE INVENTION

The present invention provides pharmaceutical compositions and methods for improved delivery of ionizable hydrophobic therapeutic agents.

In one embodiment, the invention is directed to a pharmaceutical composition including an ionizable hydrophobic therapeutic agent and a carrier. The carrier includes an ionizing agent to ionize the therapeutic agent, and a surfactant. Optionally, the carrier also includes solubilizers, triglycerides and neutralizing agents.

In another embodiment, the invention is directed to a pharmaceutical composition including a hydrophobic therapeutic agent having at least one ionizable functional group, and a carrier. The carrier includes an ionizing agent capable of ionizing the functional group, a surfactant, and a triglyceride.

In another embodiment, the invention is directed to a pharmaceutical composition including a hydrophobic therapeutic agent having at least one ionizable functional group and a carrier, wherein the carrier includes an ionizing agent capable of ionizing the ionizable functional group and present in a pre-reaction amount of greater than about 1.5 mole equivalents per mole of ionizable functional group, and a surfactant. In a further aspect of this embodiment, the composition further includes a neutralizing agent capable of neutralizing a portion of the ionizing agent.

In another embodiment, the invention is directed to a pharmaceutical composition including a hydrophobic therapeutic agent having at least one ionizable functional group, and a carrier, wherein the carrier includes an ionizing agent capable of ionizing the ionizable functional group, a surfactant, and a solubilizer present in an amount of greater than about 10% by weight, based on the total weight of the composition. In this embodiment, the surfactant includes at least one compound from the group consisting of alkylglucosides; alkylmaltosides; alkylthioglucosides; lauryl macrogolglycerides; polyoxyethylene alkyl ethers; fatty acids; lower alcohol fatty acid esters; polyoxyethylene alkylphenols; polyethylene glycol fatty acids esters; polypropylene glycol fatty acid esters; glycerol fatty acid esters; acetylated glycerol fatty acid esters; polyethylene glycol glycerol fatty acid esters; polyglyceryl fatty acid esters;

polyoxyethylene glycerides; polyoxyethylene sterols, derivatives, and analogues thereof; polyoxyethylene vegetable oils; polyoxyethylene hydrogenated vegetable oils; reaction mixtures of polyols and at least one member of the group consisting of fatty acids, vegetable oils, hydrogenated vegetable oils, and sterols; sugar esters; sugar ethers; sucroglycerides; fatty acid salts; bile salts; phospholipids; phosphoric acid esters; carboxylates; sulfates; and sulfonates.

In another embodiment, the present invention is directed to a pharmaceutical composition including a hydrophobic therapeutic agent having at least one ionizable functional group and a carrier, wherein the carrier includes an ionizing agent capable of ionizing the ionizable functional group, a surfactant, and a solubilizer. In this embodiment, the surfactant includes at least one compound selected from the group consisting of alkylglucosides; alkylmaltosides; alkylthioglucosides; lauryl macrogolglycerides; fatty acids; lower alcohol fatty acid esters; polyoxyethylene alkylphenols; polyethylene glycol fatty acids esters; polypropylene glycol fatty acid esters; glycerol fatty acid esters; acetylated glycerol fatty acid esters; polyethylene glycol glycerol fatty acid esters; polyglyceryl fatty acid esters; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene glycerides; polyoxyethylene sterols, derivatives, and analogues thereof; polyoxyethylene vegetable oils; polyoxyethylene hydrogenated vegetable oils; reaction mixtures of polyols and at least one member of the group consisting of fatty acids, vegetable oils, hydrogenated vegetable oils, and sterols; sugar esters; sugar ethers; sucroglycerides; fatty acid salts; bile salts; phospholipids; phosphoric acid esters; carboxylates; sulfates; and sulfonates.

The solubilizer in this embodiment includes at least one compound selected from the group consisting of alcohols, polyols, amides, esters, and propylene glycol ethers, the alcohol or polyol being selected from the group consisting of ethanol, isopropanol, butanol, benzyl alcohol, ethylene glycol, propylene glycol, butanediols and isomers thereof, glycerol, pentaerythritol, sorbitol, mannitol, dimethyl isosorbide, polypropylene glycol, polyvinylalcohol, hydroxypropyl methylcellulose and other cellulose derivatives, maltodextrins, and cyclodextrins and cyclodextrin derivatives.

In another embodiment, the present invention provides a method of preparing a pharmaceutical composition of an ionizable hydrophobic therapeutic agent. In this embodiment, the method includes the steps of: providing a pharmaceutical composition having an ionizable hydrophobic therapeutic agent and a carrier which includes an

ionizing agent and a surfactant; and providing a neutralizing agent to neutralize at least a portion of the ionizing agent.

In another embodiment, the present invention provides a method of treating an animal with an ionizable hydrophobic therapeutic agent. The method includes the steps of providing a pharmaceutical composition having an ionizable hydrophobic therapeutic agent and a carrier which includes an ionizing agent and a surfactant; and administering the pharmaceutical composition to an animal.

These features of the present invention will become more fully apparent from the following description and appended claims, or may be learned by the practice of the invention as set forth hereinafter.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention overcomes the problems described above characteristic of conventional formulations, by providing pharmaceutical compositions including an ionizable hydrophobic therapeutic agent and a carrier. The carrier includes a surfactant, and an ionizing agent capable of ionizing the ionizable hydrophobic therapeutic agent. Optional components include one or more additional surfactants, solubilizers, triglycerides, neutralizing agents, and various additives. The carrier is able to solubilize the ionizable hydrophobic therapeutic agent and maintain the therapeutic agent in solubilized form for improved delivery to the absorption site. The invention also encompasses various dosage forms of the pharmaceutical composition.

The present invention further provides a method of solubilizing ionizable hydrophobic therapeutic agents for improved performance in pharmaceutical compositions. The method includes the steps of providing a pharmaceutical composition as described above, and providing a neutralizing agent to neutralize a portion of the ionizing agent.

1. Ionizable Hydrophobic Therapeutic Agents

Ionizable hydrophobic therapeutic agents suitable for use in the pharmaceutical compositions of the present invention are not particularly limited, as the carrier is surprisingly capable of solubilizing and delivering a wide variety of ionizable hydrophobic therapeutic agents. Ionizable hydrophobic therapeutic agents are compounds with little or no water solubility at neutral pH. Intrinsic water solubilities (*i.e.*, water solubility of the unionized form) for the ionizable hydrophobic therapeutic agents usable in the present invention are less than about 1% by weight, and typically

less than about 0.1% or 0.01% by weight. Such therapeutic agents can be any agents having therapeutic or other value when administered to an animal, particularly to a mammal, such as drugs, nutrients, and cosmetics (cosmeceuticals). It should be understood that while the invention is described with particular reference to its value in oral dosage form, the invention is not so limited. Thus, ionizable hydrophobic drugs, nutrients or cosmetics which derive their therapeutic or other value from, for example, topical or transdermal administration, are still considered to be suitable for use in the present invention.

It is a particular feature of the present invention that a wide variety of therapeutic agents can be effectively incorporated in and delivered by the present pharmaceutical compositions. The essential feature of a suitable therapeutic agent is the presence of at least one ionizable functional group. Ionizable functional groups can be acidic groups, or basic groups, with "acidic" and "basic" referring to acidic or basic behavior in a Brønsted-Lowry or Lewis acid/base sense. Acidic functional groups are those groups that can be deprotonated by a suitable base to yield the corresponding anionic group (the conjugate base), or groups that can accept an electron pair. Basic functional groups are those groups that can be protonated by a suitable acid to yield the corresponding cationic group (the conjugate acid), or can donate an electron pair. It should be appreciated that the suitability of a therapeutic agent for use in the methods and compositions of the present invention is not determined by its therapeutic class, but is instead determined by the acid-base properties of its acidic or basic functional groups.

The terms "acid" and "base" as used herein refer to the ability of a functional group to act as a Brønsted-Lowry acid or Lewis acid, or as a Brønsted-Lowry base or Lewis base, in the presence of an appropriate ionizing agent. For simplicity, the acidic and basic properties of functional groups, ionizing agents, and neutralizing agents are described herein with particular reference to Brønsted-Lowry properties, but the corresponding Lewis acid/base properties are also included within the scope of these terms.

This usage should be contrasted with the terminology typically used in describing whether a compound is "acidic" or "basic" based on the pK_a of the compound in deionized water. For example, the equivalent pK_a of a functional group need not be less than 7 to be considered "acidic", since even functional groups with a large pK_a can be "acidic" if they can be deprotonated by a strong base. Similarly, a functional group with

an equivalent pK_a of less than 7 may still be considered "basic" if it can be protonated by a stronger acid. Thus, it is the ability of a particular functional group to be ionized (protonated or deprotonated) by a suitable ionizing agent (acid or base) that determines whether a functional group is acidic or basic, rather than the particular pK_a associated with that group or with the compound as a whole.

As a specific example, itraconazole is a hydrophobic therapeutic agent having a pK_a of 3.7, and a pK_b of 10.3. Thus, itraconazole can be protonated by an acid having a pK_a less than 3.7, or deprotonated by a base having a pK_b less than 10.3.

Suitable therapeutic agents contain at least one ionizable functional group. Of course, many suitable therapeutic agents contain a plurality of such groups, and a single therapeutic agent may contain one or more acidic functional groups as well as one or more basic functional groups. Such therapeutic agents are also within the scope of the present invention.

Acidic functional groups include, but are not limited to, carboxylic acids, imidazolidinediones, thiazolidinediones, pyrimidinetriones, hydroxyheteroaromatics, phenols, phosphoric acids, sulfuric acids, sulfonic acids, sulfonamides, aminosulfones, sulfonylureas, tetrazoles and thiols.

In order to avoid particularly cumbersome terminology, the functional groups, whether acidic or basic, are referred to by naming the corresponding free compound. For example, referring to a functional group, the term "aminosulfone" is used, rather than the more technically precise term "aminosulfonyl". This usage is common in the art, and is well understood by one skilled in the art.

Basic functional groups include, but are not limited to, aliphatic amines, aromatic amines, *C*-substituted aromatic amines, *N*-substituted aromatic amines, heterocyclic amines, *C*-substituted heterocyclic amines and *N*-substituted heterocyclic amines.

Examples of aromatic amines and substituted aromatic amines include, but are not limited to, aniline, *N*-methylaniline and *p*-toluidine.

Examples of heterocyclic and substituted heterocyclic amines include, but are not limited to, pyrrole, pyrazole, imidazole, indole, pyridine, pyridazine, pyrimidine, quinoline, piperidine, pyrrolidine, morpholine, thiazole, purine and triazole.

Specific examples of suitable therapeutic agents having at least one ionizable acidic functional group include, but are not limited to: acetazolamide, acetohexamide, acrivastine, alatrofloxacin, albuterol, alclofenac, aloxiprin, alprostadil, amodiaquine,

amphotericin, amylobarbital, aspirin, atorvastatin, atovaquone, baclofen, barbital, benezepril, bezafibrate, bromfenac, bumetanide, butobarbital, candesartan, capsacin, captopril, cefazolin, celecoxib, cephadrine, cephalexin, cerivistatin, cetrizine, chlorambucil, chlorothiazide, chlorpropamide, chlorthalidone, cinoxacin, ciprofloxacin, clinofibrate, cloxacillin, cromoglicate, cromolyn, dantrolene, dichlorophen, diclofenac, dicloxacillin, dicumarol, diflunisal, dimenhydrinate, divalproen, docusate, dronabinol, enoximone, enalapril, enoxacin, enrofloxacin, epalrestate, eposartan, essential fatty acids, estramustine, ethacrynic acid, ethotoin, etodolac, etoposide, fenbufen, fenoprofen, fexofenadine, fluconazole, flurbiprofen, fluvastatin, fosinopril, fosphenytoin, fumagillin, furosemide, gabapentin, gemfibrozil, gliclazide, glipizide, glybenclamide, glyburide, glymepiride, grepafloxacin, ibufenac, ibuprofen, imipenem, indomethacin, irbesartan, isotretinoin, ketoprofen, ketorolac, lamotrigine, levofloxacin, levothyroxine, lisinopril, lomefloxacin, losartan, lovastatin, meclofenamic acid, mefenamic acid, mesalamine, methotrexate, metolazone, montelukast, nalidixic acid, naproxen, natamycin, nimesulide, nitrofurantoin, non-essential fatty acids, norfloxacin, nystatin, ofloxacin, oxacillin, oxaprozin, oxyphenbutazone, penicillins, pentobarbital, perfloxacin, phenobarbital, phenytoin, pioglitazone, piroxicam, pramipexol, pranlukast, pravastatin, probenecid, probucol, propofol, propylthiouracil, quinapril, rabeprazole, repaglinide, rifampin, rifapentine, sparfloxacin, sulfabenzamide, sulfacetamide, sulfadiazine, sulfadoxine, sulfamerazine, sulfamethoxazole, sulfafurazole, sulfapyridine, sulfasalazine, sulindac, sulphasalazine, sulthiame, telmisartan, teniposide, terbutaline, tetrahydrocannabinol, tirofiban, tolazamide, tolbutamide, tolcapone, tolmetin, tretinoin, troglitazone, trovafloxacin, undecenoic acid, ursodeoxycholic acid, valproic acid, valsartan, vancomycin, verteporfin, vigabatrin, vitamin K-S (II) and zafirlukast.

Among the above-listed hydrophobic therapeutic agents having at least one acidic functional group, preferred hydrophobic therapeutic agents are: acetohexamide, acrivastine, alatrofloxacin, albuterol, alclofenac, amodiaquine, amphotericin, aspirin, atorvastatin, atovaquone, baclofen, benezepril, bezafibrate, bromfenac, butobarbital, candesartan, capsacin, captopril, celecoxib, cerivistatin, cetrizine, chlorambucil, chlorpropamide, chlorthalidone, clinofibrate, cinoxacin, ciprofloxacin, clinofibrate, cloxacillin, cromoglicate, cromolyn, dantrolene, diclofenac, dicumarol, divalproen, docusate, dronabinol, enalapril, enoxacin, eposartan, etodolac, etoposide, fenbufen, fenoprofen, fexofenadine, fluconazole, flurbiprofen, fluvastatin, fosphenytoin,

fumagillin, gabapentin, gemfibrozil, gliclazide, glipizide, glyburide, glymepiride, grepafloxacin, ibufenac, ibuprofen, imipenem, indomethacin, irbesartan, isotretinoin, ketoprofen, ketorolac, lamotrigine, levofloxacin, levothyroxine, lisinopril, lomefloxacin, losartan, lovastatin, mesalamine, methotrexate, montelukast, naproxen, nimesulide, non-essential fatty acids, norfloxacin, ofloxacin, oxaprozin, phenytoin, pioglitazone, piroxicam, pramipexol, pravastatin, probucol, propofol, rabeprazole, repaglinide, rifampin, rifapentine, sparfloxacin, sulfadiazine, sulfamethoxazole, sulfasalazine, sulindac, sulphasalazine, telmisartan, teniposide, terbutaline, tetrahydrocannabinol, tirofiban, tolazamide, tolbutamide, tolcapone, tolmetin, tretinoin, troglitazone, trovafloxacin, undecenoic acid, valproic acid, valsartan, vancomycin, verteporfin, vigabatrin, vitamin K-S (II) and zafirlukast.

Among the preferred hydrophobic therapeutic agents having at least one ionizable acidic functional group, the more preferred hydrophobic therapeutic agents are: acrivastine, alatrofloxacin, albuterol, alclofenac, aspirin, atorvastatin, atovaquone, baclofen, benezepril, bezafibrate, bromfenac, butobarbital, celecoxib, cerivistatin, cetrizine, chlorpropamide, ciprofloxacin, cromoglicate, cromolyn, dantrolene, diclofenac, dicumarol, divalproen, dronabinol, enoxacin, etodolac, etoposide, fenoprofen, fexofenadine, fluconazole, flurbiprofen, fluvastatin, fosphenytoin, gemfibrozil, glipizide, glyburide, glymepiride, grepafloxacin, ibufenac, ibuprofen, isotretinoin, ketoprofen, ketorolac, lamotrigine, levofloxacin, levothyroxine, lomefloxacin, lovastatin, methotrexate, montelukast, naproxen, nimesulide, non-essential fatty acids, norfloxacin, ofloxacin, oxaprozin, phenytoin, pioglitazone, piroxicam, pravastatin, probucol, rabeprazole, repaglinide, rifampin, rifapentine, sulfamethoxazole, sulfasalazine, teniposide, tetrahydrocannabinol, tolcapone, tolmetin, tretinoin, troglitazone, trovafloxacin, valproic acid, vancomycin, vitamin K-S (II) and zafirlukast.

The most preferred hydrophobic therapeutic agents having at least one ionizable acidic functional group are: alclofenac, aspirin, atorvastatin, atovaquone, benezepril, bromfenac, celecoxib, cromoglicate, cromolyn, diclofenac, dronabinol, etodolac, fexofenadine, flurbiprofen, glymepiride, ibufenac, ibuprofen, isotretinoin, ketoprofen, ketorolac, levothyroxine, naproxen, non-essential fatty acids, oxaprozin, phenytoin, pioglitazone, rabeprazole, repaglinide, teniposide, tetrahydrocannabinol, tolmetin, tretinoin, troglitazone, trovafloxacin and vitamin K-S (II).

Specific examples of suitable hydrophobic therapeutic agents having at least one ionizable basic functional group include, but are not limited to: abacavir, acebutolol, acrivastine, alatrofloxacin, albuterol, albendazole, alprazolam, alprenolol, amantadine, amiloride, aminoglutethimide, amiodarone, amitriptyline, amlodipine, amodiaquine, amoxapine, amphetamine, amphotericin, amprenavir, amrinone, amsacrine, astemizole, atenolol, atropine, azathioprine, azelastine, azithromycin, baclofen, benethamine, benidipine, benzhexol, benznidazole, benztropine, biperiden, bisacodyl, bisanthrene, bromazepam, bromocriptine, bromperidol, brompheniramine, brotizolam, bupropion, butenafine, butoconazole, cambendazole, camptothecin, carbinoxamine, cephadrine, cephalexin, cetrizine, cinnarizine, chlorambucil, chlopheniramine, chloproguanil, chlordiazepoxide, chlorpromazine, chlorprothixene, chloroquine, cimetidine, ciprofloxacin, cisapride, citalopram, clarithromycin, clemastine, clemizole, clenbuterol, clofazimine, clomiphene, clonazepam, clopidrogel, clozapine, clotiazepam, clotrimazole, codeine, cyclizine, cyproheptadine, dacarbazine, darodipine, decoquinate, delavirdine, demeclocycline, dexamphetamine, dexchlopheniramine, dexfenfluramine, diamorphine, diazepam, diethylpropion, dihydrocodeine, dihydroergotamine, dilitazem, dimenhydrinate, diphenhydramine, diphenooxylate, diphenylimidazole, diphenylpyrallin, dipyridamole, dirithromycin, disopyramide, dolasetron, domperidone, donepezil, doxazosin, doxycycline, droperidol, econazole, efavirenz, ellipticine, enalapril, enoxacin, enrofloxacin, eperisone, ephedrine, ergotamine, erythromycin, ethambutol, ethionamide; ethopropazine, etoperidone, famotidine, felodipine, fenbendazole, fenfluramine, fenoldopam, fentanyl, fexofenadine, flecainide, flucytosine, flunarizine, flunitrazepam, fluopromazine, fluoxetine, flupentixol, flupentixol decanoate, fluphenazine, fluphenazine decanoate, flurazepam, flurithromycin, frovatriptan, gabapentin, granisetron, grepafloxacin, guanabenz, halofantrine, haloperidol, hyoscyamine, imipenem, indinavir, irinotecan, isoxazole, isradipine, itraconazole, ketoconazole, ketotifen, labetalol, lamivudine, lanosprazole, leflunomide, levofloxacin, lisinopril, lomefloxacin, loperamide, loratadine, lorazepam, lormetazepam, lysuride, mepacrine, maprotiline, mazindol, mebendazole, meclozine, medazepam, mefloquine, melonicam, meptazinol, mercaptopurine, mesalamine, mesoridazine, metformin, methadone, methaqualone, methylphenidate, methylphenobarbital, methysergide, metoclopramide, metoprolol, metronidazole, mianserin, miconazole, midazolam, miglitol, minoxidil, mitomycins, mitoxantrone, molindone, montelukast, morphine, mortriptyline, moxifloxacin, nadolol,

nalbuphine, naratriptan, natamycin, nefazodone, nelfinavir, nevirapine, nicardipine, nicotine, nifedipine, nimodipine, nimorazole, nisoldipine, nitrazepam, nitrofurazone, nizatidine, norfloxacin, nystatin, ofloxacin, olanzapine, omeprazole, ondansetron, ornidazole, oxamniquine, oxantel, oxatomide, oxazepam, oxfendazole, oxiconazole, oxprenolol, oxybutynin, oxyphencylcimine, paroxetine, pentazocine, pentoxifylline, perchloperazine, perfloxacin, perphenazine, phenbenzamine, pheniramine, phenoxybenzamine, phentermine, physostigmine, pimozide, pindolol, pizotifen, pramipexol, pranlukast, praziquantel, prazosin, procarbazine, prochlorperazine, proguanil, propranolol, pseudoephedrine, pyrantel, pyrimethamine, quetiapine, quinidine, quinine, raloxifene, ranitidine, remifentanil, repaglinide, reserpine, ricobendazole, rifabutin, rifampin, rifapentine, rimantadine, risperidone, ritonavir, rizatriptan, ropinirole, rosiglitazone, roxatidine, roxithromycin, salbutamol, saquinavir, selegiline, sertraline, sibutramine, sildenafil, sparfloxacin, spiramycins, stavudine, sulconazole, sulphasalazine, sulpiride, sumatriptan, tacrine, tamoxifen, tamsulosin, temazepam, terazosin, terbinafine, terbutaline, terconazole, terfenadine, tetramisole, thiabendazole, thioguanine, thioridazine, tiagabine, ticlopidine, timolol, tinidazole, tioconazole, tirofiban, tizanidine, tolterodine, topotecan, toremifene, tramadol, trazodone, triamterene, triazolam, trifluoperazine, trimethoprim, trimipramine, tromethamine, tropicamide, trovafloxacin, vancomycin, venlafaxine, vigabatrin, vinblastine, vincristine, vinorelbine, vitamin K_5, vitamin K_6, vitamin K_7, zafirlukast, zolmitriptan, zolpidem and zopiclone.

Among the above-listed hydrophobic therapeutic agents having at least one ionizable basic functional group, preferred hydrophobic therapeutic agents are: abacavir, acebutolol, acrivastine, alatrofloxacin, albendazole, albuterol, alprazolam, amiodarone, amlodipine, amodiaquine, amphetamine, amphotericin, amprenavir, astemizole, atenolol, azathioprine, azelastine, azithromycin, baclofen, benztropine, bisacodyl, bromazepam, bromperidol, brompheniramine, bupropion, butenafine, butoconazole, cambendazole, camptothecin, carbinoxamine, cetrizine, cinnarizine, chlopheniramine, chlorambucil, chlorpromazine, cimetidine, ciprofloxacin, cisapride, citalopram, clarithromycin, clemastine, clemizole, clomiphene, clonazepam, clopidrogel, clozapine, clotiazepam, clotrimazole, codeine, cyclizine, delavirdine, dexamphetamine, dexchlopheniramine, diamorphine, diazepam, diethylpropion, dihydrocodeine, dihydroergotamine, dilitazem, diphenhydramine, diphenylimidazole, diphenylpyrallin, dipyridamole, dirithromycin, disopyramide, dolasetron, domperidone, donepezil, doxazosin, droperidol, econazole,

efavirenz, ellipticine, enalapril, enoxacin, eperisone, ergotamine, famotidine, felodipine, fenfluramine, fenoldopam, fexofenadine, fentanyl, flecainide, flunarizine, fluopromazine, fluoxetine, frovatriptan, gabapentin, granisetron, halofantrine, imipenem, indinavir, irinotecan, isoxazole, isradipine, itraconazole, ketoconazole, ketotifen, labetalol, lamivudine, lanosprazole, leflunomide, levofloxacin, lisinopril, lomefloxacin, loperamide, loratadine, lorazepam, lormetazepam, mazindol, mebendazole, mefloquine, mercaptopurine, mesalamine, metformin, methadone, methaqualone, methylphenidate, methysergide, metoclopramide, metoprolol, metronidazole, miconazole, midazolam, miglitol, minoxidil, mitoxantrone, montelukast, naratriptan, nelfinavir, nevirapine, nicardipine, nicotine, nifedipine, nimodipine, nimorazole, nisoldipine, nizatidine, norfloxacin, ofloxacin, olanzapine, omeprazole, ondansetron, oxamniquine, oxiconazole, paroxetine, perchloperazine, phenbenzamine, pheniramine, phentermine, physostigmine, pizotifen, pramipexol, prazosin, prochlorperazine, pseudoephedrine, quetiapine, quinidine, raloxifene, ranitidine, remifentanil, repaglinide, rifabutin, rifampin, rifapentine, rimantadine, risperidone, ritonavir, rizatriptan, rosiglitazone, roxatidine, saquinavir, sibutramine, sildenafil, sparfloxacin, stavudine, sulphasalazine, sumatriptan, tacrine, tamoxifen, tamsulosin, terazosin, terbinafine, terbutaline, terconazole, terfenadine, tiagabine, ticlopidine, tinidazole, tioconazole, tirofiban, tizanidine, tolterodine, topotecan, toremifene, tramadol, trazodone, trovafloxacin, vancomycin, venlafaxine, vigabatrin, vinblastine, vincristine, vinorelbine, vitamin K_5, vitamin K_6, vitamin K_7, zafirlukast, zolmitriptan, zolpidem and zopiclone.

Among the preferred hydrophobic therapeutic agents having at least one ionizable basic functional group, more preferred hydrophobic therapeutic agents are: abacavir, acrivastine, alatrofloxacin, albuterol, amiodarone, amlodipine, amphetamine, amprenavir, astemizole, atenolol, azathioprine, azelastine, azithromycin, baclofen, benztropine, bisacodyl, bromazepam, bromperidol, brompheniramine, bupropion, butenafine, butoconazole, cambendazole, camptothecin, carbinoxamine, cetrizine, cinnarizine, chlopheniramine, chlorpromazine, cimetidine, ciprofloxacin, cisapride, clarithromycin, clemastine, clemizole, clonazepam, clopidrogel, clotrimazole, codeine, dexchlopheniramine, dihydrocodeine, dihydroergotamine, diphenhydramine, diphenylimidazole, diphenylpyrallin, dirithromycin, dolasetron, domperidone, doxazosin, econazole, efavirenz, ellipticine, enoxacin, eperisone, ergotamine, famotidine, fenoldopam, fentanyl, fexofenadine, flunarizine, fluoxetine, frovatriptan, granisetron,

grepafloxacin, halofantrine, indinavir, irinotecan, isradipine, itraconazole, ketoconazole, ketotifen, lamivudine, lanosprazole, leflunomide, levofloxacin, loperamide, loratadine, metformin, methadone, methylphenidate, methysergide, metronidazole, miconazole, midazolam, miglitol, mitoxantrone, montelukast, naratriptan, nelfinavir, nicotine, nifedipine, nimorazole, nizatidine, norfloxacin, ofloxacin, omeprazole, ondansetron, perchloperazine, phenbenzamine, physostigmine, pizotifen, pseudoephedrine, quetiapine, quinidine, raloxifene, ranitidine, remifentanil, repaglinide, rifabutin, rifampin, rifapentine, rimantadine, ritonavir, rizatriptan, rosiglitazone, roxatidine, saquinavir, sibutramine, sildenafil, stavudine, sumatriptan, tacrine, tamoxifen, tamsulosin, terazosin, terbinafine, tinidazole, tizanidine, tolterodine, topotecan, toremifene, tramadol, trovafloxacin, vancomycin, vinblastine, vincristine, vinorelbine, vitamin K_5, vitamin K_6, vitamin K_7, zafirlukast, zolmitriptan and zolpidem.

The most preferred hydrophobic therapeutic agents having at least one ionizable basic functional group are: amlodipine, astemizole, brompheniramine, bupropion, carbinoxamine, cetrizine, cimetidine, cisapride, clemastine, clemizole, dihydroergotamine, diphenhydramine, diphenylimidazole, diphenylpyrallin, domperidone, famotidine, fexofenadine, frovatriptan, granisetron, itraconazole, ketoconazole, ketotifen, lanosprazole, leflunomide, loperamide, loratadine, methysergide, miglitol, montelukast, naratriptan, nizatidine, omeprazole, ondansetron, phenbenzamine, pseudoephedrine, raloxifene, ranitidine, repaglinide, rifabutin, rimantadine, ritonavir, rizatriptan, rosiglitazone, roxatidine, saquinavir, sibutramine, sildenafil, sumatriptan, tamsulosin, terbinafine, tizanidine, tramadol, trovafloxacin, vitamin K_5, vitamin K_6, vitamin K_7, zafirlukast, zolmitriptan and zolpidem.

Also included within the scope of the invention are pharmaceutically equivalent derivatives and/or analogs of the ionizable hydrophobic therapeutic agents. Such equivalents include salts, esters, alkyl and acyl derivatives, liposome-encapsulated derivatives, o/w emulsions of derivatives, and the like.

In particular, salts of ionizable hydrophobic therapeutic agents are suitable for use in the present invention. Salts may be used advantageously for the sake of salt exchange with the acid or base ionizing agent, leading to better salt selection.

It should be appreciated that this listing of ionizable hydrophobic therapeutic agents is merely illustrative. Indeed, a particular feature, and surprising advantage, of the compositions of the present invention is the ability of the present compositions to

solubilize and deliver a broad range of ionizable hydrophobic therapeutic agents, regardless of therapeutic class. Of course, mixtures of ionizable hydrophobic therapeutic agents may also be used where desired.

The amount of hydrophobic therapeutic agent to be used depends upon the dosage amount to be delivered. One skilled in the art can determine the appropriate dosage amount, depending upon the specific hydrophobic therapeutic agent to be delivered, the nature of the condition treated, the relative efficacy of the therapeutic agent, and other factors commonly considered. The compositions of the present invention can contain a therapeutically effective amount of the therapeutic agent, up to the amount of therapeutic agent that can be solubilized in the carrier. In addition, if desired the compositions can further contain an additional amount of the hydrophobic therapeutic agent suspended (not solubilized) in the carrier.

2. **Ionizing Agents**

The ionizing agent can be any pharmaceutically acceptable acid or base capable of protonating or deprotonating the ionizable functional groups of the ionizable hydrophobic therapeutic agent, in a Brønsted-Lowry sense, or capable of accepting or donating an electron pair, in a Lewis sense. For convenience, the ionizing agents are discussed in terms of Brønsted-Lowry properties, although Lewis acids and bases are also suitable ionizing agents.

Ionizing agents that deprotonate the acidic functional groups of the therapeutic agent are pharmaceutically acceptable organic or inorganic bases. Examples of such bases include amino acids, amino acid esters, ammonium hydroxide, potassium hydroxide, sodium hydroxide, sodium hydrogen carbonate, aluminum hydroxide, calcium carbonate, magnesium hydroxide, magnesium aluminum silicate, synthetic aluminum silicate, synthetic hydrotalcite, magnesium aluminum hydroxide, diisopropylethylamine, ethanolamine, ethylenediamine, triethanolamine, triethylamine, triisopropanolamine, and the like. Also suitable are bases which are salts of a pharmaceutically acceptable acid, such as acetic acid, acrylic acid, adipic acid, alginic acid, alkanesulfonic acid, amino acids, ascorbic acid, benzoic acid, boric acid, butyric acid, carbonic acid, citric acid, fatty acids, formic acid, fumaric acid, gluconic acid, hydroquinosulfonic acid, isoascorbic acid, lactic acid, maleic acid, oxalic acid, para-bromophenylsulfonic acid, propionic acid, p-toluenesulfonic acid, salicylic acid, stearic acid, succinic acid, tannic acid, tartaric acid, thioglycolic acid, toluenesulfonic acid, uric

acid, and the like. Salts of polyprotic acids, such as sodium phosphate, disodium hydrogen phosphate, and sodium dihydrogen phosphate can also be used. When the base is a salt, the cation can be any convenient and pharmaceutically acceptable cation, such as ammonium, alkali metals, alkaline earth metals, and the like. Preferred cations include sodium, potassium, lithium, magnesium, calcium and ammonium.

Ionizing agents that protonate the basic functional groups of the therapeutic agent are pharmaceutically acceptable inorganic or organic acids. Examples of suitable inorganic acids include hydrochloric acid, hydrobromic acid, hydriodic acid, sulfuric acid, nitric acid, boric acid, phosphoric acid, and the like. Examples of suitable organic acids include acetic acid, acrylic acid, adipic acid, alginic acid, alkanesulfonic acid, amino acids, ascorbic acid, benzoic acid, boric acid, butyric acid, carbonic acid, citric acid, fatty acids, formic acid, fumaric acid, gluconic acid, hydroquinosulfonic acid, isoascorbic acid, lactic acid, maleic acid, methanesulfonic acid, oxalic acid, para-bromophenylsulfonic acid, propionic acid, p-toluenesulfonic acid, salicylic acid, stearic acid, succinic acid, tannic acid, tartaric acid, thioglycolic acid, toluenesulfonic acid, uric acid and the like. Of course, the distinction between inorganic and organic acids is not particularly important, but is provided merely as a convenient and conventional way to classify the acids.

In one embodiment, the ionizing agent is present in an amount sufficient to ionize at least a portion of the ionizable functional groups. In this embodiment, the ionizing agent preferably is present in an amount of at least about 0.1 mole equivalents per mole of ionizable functional groups. The term "mole equivalents" as used herein means the number of moles of ionizing functionality effectively presented by the ionizing agent. Thus, for example, when the ionizing agent is a diprotic acid capable of ionizing two moles of basic functional groups per mole of the diprotic acid, only 0.5 moles of the ionizing agent per mole of ionizable functional groups is necessary to provide 1.0 mole equivalents of ionizing agent.

Whether a particular acid is diprotic or polyprotic for purposes of determining the number of mole equivalents for a given concentration depends upon the basicity of the functional group to be ionized. Thus, for example, phosphoric acid is potentially a tri-protic acid, capable of protonating three moles of functional groups per mole of phosphoric acid, in successive ionization steps:

$$H_3PO_4 \leftrightarrows H_2PO_4^- + H^+ \qquad pK_a = 2.2$$
$$H_2PO_4^- \leftrightarrows HPO_4^{2-} + H^+ \qquad pK_a = 7.2$$
$$HPO_4^{2-} \leftrightarrows PO_4^{3-} + H^+ \qquad pK_a = 11.2$$

Representing the ionizable basic therapeutic agent as "D", the corresponding ionization reaction is:

$$D + H^+ \leftrightarrows DH^+ \qquad pK_b \text{ of } D$$

Each successive ionization step will only occur, however, if the pK_a of the acid is less than the pK_a of the therapeutic agent. Thus, when the therapeutic agent is, for example, itraconazole, with a pK_a of 3.7, only the first reaction will occur to any appreciable extent. With respect to itraconazole, phosphoric acid behaves as a monoprotic acid, and one mole of phosphoric acid provides one mole equivalent of ionizing agent. Similar considerations apply when the ionizing agent is a base, and the ionizable functional group is acidic.

In one embodiment of the invention, the ionizing agent is present in an amount of at least about 0.1 mole equivalents per mole of ionizable functional group. Preferably, the ionizing agent is present in an amount of at least about 0.2 mole equivalents per mole of ionizable functional group, more preferably at least about 0.5 mole equivalents.

When the pharmaceutical composition is intended for formulation in a dosage form that shows poor compatibility with the ionizing agent, such as a gelatin capsule, the ionizing agent is preferably present in an amount of less than about 1.5 mole equivalents per mole of ionizable functional group, and more preferably less than about 1.0 mole equivalents.

In another embodiment of the invention, the ionizing agent is present in an amount of greater than about 1.0 mole equivalents per mole of ionizable functional group. In a further embodiment of the invention, the ionizing agent is present in an amount of greater than about 1.5 mole equivalents per mole of ionizable functional group.

The use of an excess (*i.e.*, greater than 1.0 mole equivalents or greater than 1.5 mole equivalents) of ionizing agent presents several advantages. Since solubilization of the hydrophobic therapeutic agent depends upon the therapeutic agent being ionized, a higher concentration of ionizing agent provides a greater extent of ionization and thus increased solubilization. This increased solubilization is particularly important when the acid or base ionization constants (K_a or K_b) of the ionizing agent and the therapeutic

agent are similar in magnitude. For example, when the ionization constants are within about an order of magnitude of each other, the ionized and un-ionized forms of the therapeutic agent will be in equilibrium, with a significant amount of the therapeutic agent being present in the un-ionized form. When the ionization constants differ by about two or more orders of magnitude, an equilibrium is still present, but the amount of non-ionized therapeutic agent will be negligibly small.

A further advantage of using an excess of ionizing agent is in ease of preparation. Higher concentrations of ionizing agent facilitate rapid and complete solubilization, making the preparation of solubilized therapeutic agent easier and more efficient, thereby conserving expensive manufacturing and personnel resources.

In addition, it is believed that higher levels of ionizing agent, when used in the compositions of the present invention, advantageously promote continued solubilization of the therapeutic agent, both for storage of the composition, as well as in the gastrointestinal tract upon administration of the composition to a patient.

Although use of higher levels of ionizing agent in the compositions of the present invention presents several advantages, such higher levels are known to be poorly compatible with conventional gelatin capsule dosage forms. Thus, when the dosage form is a gelatin capsule containing the pharmaceutical compositions of the present invention, it is desirable to use a smaller amount of ionizing agent. In a further embodiment of the invention, a composition of the present invention includes an ionizing agent in an amount of greater than about 1.5 mole equivalents per mole of ionizable functional group, and an amount of a neutralizing agent for the ionization agent present in an amount sufficient to at least partially neutralize the excess ionizing agent. For example, if the ionizing agent is an acid, the neutralizing agent would be a base, and vice versa. The pharmaceutically acceptable acids and bases described herein are suitable for use as the neutralizing agent in this embodiment. Thus, this embodiment provides the advantages of increased solubilization and ease of preparation resulting from a high concentration of ionizing agent, while still preserving good compatibility with conventional gelatin capsules by neutralizing some of the excess ionizing agent.

It should be emphasized that when the dosage form is, for example, a liquid drink, neutralization of excess ionizing agent may be unnecessary, and even large excesses of ionizing agent can be used. One skilled in the art can readily determine the amount of excess ionizing agent that can be used, depending upon the ultimate pH of the

solution, the degree of bioacceptability of the ionizing agent, the resultant solution taste, and other factors conventional in the art. By way of illustration only, as shown in the Examples herein, the ionizing agent can be used in an amount of several mole equivalents to tens of mole equivalents or more, per mole of ionizable functional group. These large amounts of ionizing agent can also be used when the ultimate dosage form is a gelatin capsule, or when it is desired for any reason to have a lower ionizing agent concentration, by adding a suitable neutralizing agent, as described above.

It should be understood with respect to all of the embodiments described herein that the concentration of ionizing agent given is the concentration prior to the acid-base reaction, unless otherwise noted. Of course, if the concentration of ionizing agent is, for example, 1.0 mole equivalents per mole of ionizable functional group, upon mixing of the ionizing agent and the ionizable pharmaceutical compound, an acid-base reaction will occur, and such reaction will consume some or all of the ionizing agent. Thus, a given concentration of ionizing agent refers to the pre-reaction concentration, and not to the ultimate concentration of the ionizing agent.

3. **Surfactants**

The carrier includes at least one surfactant. The surfactant can by hydrophilic, hydrophobic, or a mixture of hydrophilic and hydrophobic surfactants. As is well known in the art, the terms "hydrophilic" and "hydrophobic" are relative terms. To function as a surfactant, a compound must necessarily include polar or charged hydrophilic moieties as well as non-polar hydrophobic (lipophilic) moieties; *i.e.*, a surfactant compound must be amphiphilic. An empirical parameter commonly used to characterize the relative hydrophilicity and hydrophobicity of non-ionic amphiphilic compounds is the hydrophilic-lipophilic balance ("HLB" value). Surfactants with lower HLB values are more hydrophobic, and have greater solubility in oils, while surfactants with higher HLB values are more hydrophilic, and have greater solubility in aqueous solutions.

Using HLB values as a rough guide, hydrophilic surfactants are generally considered to be those compounds having an HLB value greater than about 10, as well as anionic, cationic, or zwitterionic compounds for which the HLB scale is not generally applicable. Similarly, hydrophobic surfactants are compounds having an HLB value less than about 10.

It should be appreciated that the HLB value of a surfactant is merely a rough guide generally used to enable formulation of industrial, pharmaceutical and cosmetic

emulsions. For many important surfactants, including several polyethoxylated surfactants, it has been reported that HLB values can differ by as much as about 8 HLB units, depending upon the empirical method chosen to determine the HLB value (Schott, *J. Pharm. Sciences*, 79(1), 87-88 (1990)). Likewise, for certain polypropylene oxide containing block copolymers (poloxamers, available commercially as PLURONIC® surfactants, BASF Corp.), the HLB values may not accurately reflect the true physical chemical nature of the compounds. Finally, commercial surfactant products are generally not pure compounds, but are often complex mixtures of compounds, and the HLB value reported for a particular compound may more accurately be characteristic of the commercial product of which the compound is a major component. Different commercial products having the same primary surfactant component can, and typically do, have different HLB values. In addition, a certain amount of lot-to-lot variability is expected even for a single commercial surfactant product. Keeping these inherent difficulties in mind, and using HLB values as a guide, one skilled in the art can readily identify surfactants having suitable hydrophilicity or hydrophobicity for use in the present invention, as described herein.

The compositions of the present invention include at least one surfactant. Suitable surfactants can be ionic hydrophilic surfactants, non-ionic hydrophilic surfactants, or hydrophobic surfactants. The surfactant can be any surfactant suitable for use in pharmaceutical compositions. Suitable hydrophilic surfactants can be anionic, cationic, zwitterionic or non-ionic, although non-ionic hydrophilic surfactants are presently preferred. Preferably, the compositions include at least one non-ionic hydrophilic surfactant. Also preferred are mixtures of two or more non-ionic hydrophilic surfactants, as well as mixtures containing at least one non-ionic hydrophilic surfactant and at least one hydrophobic surfactant.

The choice of specific surfactants should be made keeping in mind the particular hydrophobic therapeutic agent to be used in the composition, and the range of polarity appropriate for the chosen therapeutic agent. With these general principles in mind, a very broad range of surfactants is suitable for use in the present invention. Such surfactants can be grouped into the following general chemical classes detailed in the Tables herein. The HLB values given in the Tables below generally represent the HLB value as reported by the manufacturer of the corresponding commercial product. In cases where more than one commercial product is listed, the HLB value in the Tables is

the value as reported for one of the commercial products, a rough average of the reported values, or a value that, in the judgment of the present inventors, is more reliable.

It should be emphasized that the invention is not limited to the surfactants in the Tables, which show representative, but not exclusive, lists of available surfactants.

3.1. Polyethoxylated Fatty Acids

Although polyethylene glycol (PEG) itself does not function as a surfactant, a variety of PEG-fatty acid esters have useful surfactant properties. Among the PEG-fatty acid monoesters, esters of lauric acid, oleic acid, and stearic acid are most useful. Among the surfactants of Table 1, preferred hydrophilic surfactants include PEG-8 laurate, PEG-8 oleate, PEG-8 stearate, PEG-9 oleate, PEG-10 laurate, PEG-10 oleate, PEG-12 laurate, PEG-12 oleate, PEG-15 oleate, PEG-20 laurate and PEG-20 oleate. Examples of polyethoxylated fatty acid monoester surfactants commercially available are shown in Table 1.

Table 1: PEG-Fatty Acid Monoester Surfactants

COMPOUND	COMMERCIAL PRODUCT (Supplier)	HLB
PEG 4-100 monolaurate	Crodet L series (Croda)	>9
PEG 4-100 monooleate	Crodet O series (Croda)	>8
PEG 4-100 monostearate	Crodet S series (Croda), Myrj Series (Atlas/ICI)	>6
PEG 400 distearate	Cithrol 4DS series (Croda)	>10
PEG 100,200,300 monolaurate	Cithrol ML series (Croda)	>10
PEG 100,200,300 monooleate	Cithrol MO series (Croda)	>10
PEG 400 dioleate	Cithrol 4DO series (Croda)	>10
PEG 400-1000 monostearate	Cithrol MS series (Croda)	>10
PEG-1 stearate	Nikkol MYS-1EX (Nikko), Coster K1 (Condea)	2
PEG-2 stearate	Nikkol MYS-2 (Nikko)	4
PEG-2 oleate	Nikkol MYO-2 (Nikko)	4.5
PEG-4 laurate	Mapeg® 200 ML (PPG), Kessco® PEG 200ML (Stepan), LIPOPEG 2L (LIPO Chem.)	9.3

PEG-4 oleate	Mapeg® 200 MO (PPG), Kessco® PEG200 MO (Stepan),	8.3
PEG-4 stearate	Kessco® PEG 200 MS (Stepan), Hodag 20 S (Calgene), Nikkol MYS-4 (Nikko)	6.5
PEG-5 stearate	Nikkol TMGS-5 (Nikko)	9.5
PEG-5 oleate	Nikkol TMGO-5 (Nikko)	9.5
PEG-6 oleate	Algon OL 60 (Auschem SpA), Kessco® PEG 300 MO (Stepan), Nikkol MYO-6 (Nikko), Emulgante A6 (Condea)	8.5
PEG-7 oleate	Algon OL 70 (Auschem SpA)	10.4
PEG-6 laurate	Kessco® PEG300 ML (Stepan)	11.4
PEG-7 laurate	Lauridac 7 (Condea)	13
PEG-6 stearate	Kessco® PEG300 MS (Stepan)	9.7
PEG-8 laurate	Mapeg® 400 ML (PPG), LIPOPEG 4DL (Lipo Chem.)	13
PEG-8 oleate	Mapeg® 400 MO (PPG), Emulgante A8 (Condea)	12
PEG-8 stearate	Mapeg® 400 MS (PPG), Myrj 45	12
PEG-9 oleate	Emulgante A9 (Condea)	>10
PEG-9 stearate	Cremophor S9 (BASF)	>10
PEG-10 laurate	Nikkol MYL-10 (Nikko), Lauridac 10 (Croda)	13
PEG-10 oleate	Nikkol MYO-10 (Nikko)	11
PEG-10 stearate	Nikkol MYS-10 (Nikko), Coster K100 (Condea)	11
PEG-12 laurate	Kessco® PEG 600ML (Stepan)	15
PEG-12 oleate	Kessco® PEG 600MO (Stepan)	14
PEG-12 ricinoleate	(CAS # 9004-97-1)	>10
PEG-12 stearate	Mapeg® 600 MS (PPG), Kessco® PEG 600MS (Stepan)	14
PEG-15 stearate	Nikkol TMGS-15 (Nikko), Koster K15 (Condea)	14
PEG-15 oleate	Nikkol TMGO-15 (Nikko)	15

PEG-20 laurate	Kessco® PEG 1000 ML (Stepan)	17
PEG-20 oleate	Kessco® PEG 1000 MO (Stepan)	15
PEG-20 stearate	Mapeg® 1000 MS (PPG), Kessco® PEG 1000 MS (Stepan), Myrj 49	16
PEG-25 stearate	Nikkol MYS-25 (Nikko)	15
PEG-32 laurate	Kessco® PEG 1540 ML (Stepan)	16
PEG-32 oleate	Kessco® PEG 1540 MO (Stepan)	17
PEG-32 stearate	Kessco® PEG 1540 MS (Stepan)	17
PEG-30 stearate	Myrj 51	>10
PEG-40 laurate	Crodet L40 (Croda)	17.9
PEG-40 oleate	Crodet O40 (Croda)	17.4
PEG-40 stearate	Myrj 52, Emerest® 2715 (Henkel), Nikkol MYS-40 (Nikko)	>10
PEG-45 stearate	Nikkol MYS-45 (Nikko)	18
PEG-50 stearate	Myrj 53	>10
PEG-55 stearate	Nikkol MYS-55 (Nikko)	18
PEG-100 oleate	Crodet O-100 (Croda)	18.8
PEG-100 stearate	Myrj 59, Arlacel 165 (ICI)	19
PEG-200 oleate	Albunol 200 MO (Taiwan Surf.)	>10
PEG-400 oleate	LACTOMUL (Henkel), Albunol 400 MO (Taiwan Surf.)	>10
PEG-600 oleate	Albunol 600 MO (Taiwan Surf.)	>10

3.2 PEG-Fatty Acid Diesters

Polyethylene glycol fatty acid diesters are also suitable for use as surfactants in the compositions of the present invention. Representative PEG-fatty acid diesters are shown in Table 2. Among the surfactants in Table 2, preferred hydrophilic surfactants include PEG-20 dilaurate, PEG-20 dioleate, PEG-20 distearate, PEG-32 dilaurate and PEG-32 dioleate.

Table 2: PEG-Fatty Acid Diester Surfactants

COMPOUND	COMMERCIAL PRODUCT (Supplier)	HLB
PEG-4 dilaurate	Mapeg® 200 DL (PPG), Kessco® PEG 200 DL (Stepan), LIPOPEG 2-DL (Lipo Chem.)	7
PEG-4 dioleate	Mapeg® 200 DO (PPG),	6
PEG-4 distearate	Kessco® 200 DS (Stepan_	5
PEG-6 dilaurate	Kessco® PEG 300 DL (Stepan)	9.8
PEG-6 dioleate	Kessco® PEG 300 DO (Stepan)	7.2
PEG-6 distearate	Kessco® PEG 300 DS (Stepan)	6.5
PEG-8 dilaurate	Mapeg® 400 DL (PPG), Kessco® PEG 400 DL (Stepan), LIPOPEG 4 DL (Lipo Chem.)	11
PEG-8 dioleate	Mapeg® 400 DO (PPG), Kessco® PEG 400 DO (Stepan), LIPOPEG 4 DO(Lipo Chem.)	8.8
PEG-8 distearate	Mapeg® 400 DS (PPG), CDS 400 (Nikkol)	11
PEG-10 dipalmitate	Polyaldo 2PKFG	>10
PEG-12 dilaurate	Kessco® PEG 600 DL (Stepan)	11.7
PEG-12 distearate	Kessco® PEG 600 DS (Stepan)	10.7
PEG-12 dioleate	Mapeg® 600 DO (PPG), Kessco® 600 DO(Stepan)	10
PEG-20 dilaurate	Kessco® PEG 1000 DL (Stepan)	15
PEG-20 dioleate	Kessco® PEG 1000 DO (Stepan)	13
PEG-20 distearate	Kessco® PEG 1000 DS (Stepan)	12
PEG-32 dilaurate	Kessco® PEG 1540 DL (Stepan)	16
PEG-32 dioleate	Kessco® PEG 1540 DO (Stepan)	15
PEG-32 distearate	Kessco® PEG 1540 DS (Stepan)	15
PEG-400 dioleate	Cithrol 4DO series (Croda)	>10
PEG-400 distearate	Cithrol 4DS series (Croda)	>10

3.3 PEG-Fatty Acid Mono- and Di-ester Mixtures

In general, mixtures of surfactants are also useful in the present invention, including mixtures of two or more commercial surfactant products. Several PEG-fatty acid esters are marketed commercially as mixtures or mono- and diesters. Representative surfactant mixtures are shown in Table 3.

Table 3: PEG-Fatty Acid Mono- and Diester Mixtures

COMPOUND	COMMERCIAL PRODUCT (Supplier)	HLB
PEG 4-150 mono, dilaurate	Kessco® PEG 200-6000 mono, dilaurate (Stepan)	
PEG 4-150 mono, dioleate	Kessco® PEG 200-6000 mono, dioleate (Stepan)	
PEG 4-150 mono, distearate	Kessco® 200-6000 mono, distearate (Stepan)	

3.4 Polyethylene Glycol Glycerol Fatty Acid Esters

Suitable PEG glycerol fatty acid esters are shown in Table 4. Among the surfactants in the Table, preferred hydrophilic surfactants are PEG-20 glyceryl laurate, PEG-30 glyceryl laurate, PEG-40 glyceryl laurate, PEG-20 glyceryl oleate, and PEG-30 glyceryl oleate.

Table 4: PEG Glycerol Fatty Acid Esters

COMPOUND	COMMERCIAL PRODUCT (Supplier)	HLB
PEG-20 glyceryl laurate	Tagat® L (Goldschmidt)	16
PEG-30 glyceryl laurate	Tagat® L2 (Goldschmidt)	16
PEG-15 glyceryl laurate	Glycerox L series (Croda)	15
PEG-40 glyceryl laurate	Glycerox L series (Croda)	15
PEG-20 glyceryl stearate	Capmul® EMG (ABITEC), Aldo® MS-20 KFG (Lonza)	13
PEG-20 glyceryl oleate	Tagat® O (Goldschmidt)	>10
PEG-30 glyceryl oleate	Tagat® O2 (Goldschmidt)	>10

3.5. Alcohol - Oil Transesterification Products

A large number of surfactants of different degrees of hydrophobicity or hydrophilicity can be prepared by reaction of alcohols or polyalcohols with a variety of

natural and/or hydrogenated oils. Most commonly, the oils used are castor oil or hydrogenated castor oil, or an edible vegetable oil such as corn oil, olive oil, peanut oil, palm kernel oil, apricot kernel oil, or almond oil. Preferred alcohols include glycerol, propylene glycol, ethylene glycol, polyethylene glycol, sorbitol, and pentaerythritol. Among these alcohol-oil transesterified surfactants, preferred hydrophilic surfactants are PEG-35 castor oil (Incrocas-35), PEG-40 hydrogenated castor oil (Cremophor RH 40), PEG-25 trioleate (TAGAT® TO), PEG-60 corn glycerides (Crovol M70), PEG-60 almond oil (Crovol A70), PEG-40 palm kernel oil (Crovol PK70), PEG-50 castor oil (Emalex C-50), PEG-50 hydrogenated castor oil (Emalex HC-50), PEG-8 caprylic/capric glycerides (Labrasol), and PEG-6 caprylic/capric glycerides (Softigen 767). Preferred hydrophobic surfactants in this class include PEG-5 hydrogenated castor oil, PEG-7 hydrogenated castor oil, PEG-9 hydrogenated castor oil, PEG-6 corn oil (Labrafil® M 2125 CS), PEG-6 almond oil (Labrafil® M 1966 CS), PEG-6 apricot kernel oil (Labrafil® M 1944 CS), PEG-6 olive oil (Labrafil® M 1980 CS), PEG-6 peanut oil (Labrafil® M 1969 CS), PEG-6 hydrogenated palm kernel oil (Labrafil® M 2130 BS), PEG-6 palm kernel oil (Labrafil® M 2130 CS), PEG-6 triolein (Labrafil® M 2735 CS), PEG-8 corn oil (Labrafil® WL 2609 BS), PEG-20 corn glycerides (Crovol M40), and PEG-20 almond glycerides (Crovol A40). The latter two surfactants are reported to have HLB values of 10, which is generally considered to be the approximate border line between hydrophilic and hydrophobic surfactants. For purposes of the present invention, these two surfactants are considered to be hydrophobic. Representative surfactants of this class suitable for use in the present invention are shown in Table 5.

Table 5: Transesterification Products of Oils and Alcohols

COMPOUND	COMMERCIAL PRODUCT (Supplier)	HLB
PEG-3 castor oil	Nikkol CO-3 (Nikko)	3
PEG-5, 9, and 16 castor oil	ACCONON CA series (ABITEC)	6-7
PEG-20 castor oil	Emalex C-20 (Nihon Emulsion), Nikkol CO-20 TX (Nikko)	11
PEG-23 castor oil	Emulgante EL23	>10
PEG-30 castor oil	Emalex C-30 (Nihon Emulsion), Alkamuls® EL 620 (Rhone-Poulenc), Incrocas 30 (Croda)	11

PEG-35 castor oil	Cremophor EL and EL-P (BASF), Emulphor EL, Incrocas-35 (Croda), Emulgin RO 35 (Henkel)	
PEG-38 castor oil	Emulgante EL 65 (Condea)	
PEG-40 castor oil	Emalex C-40 (Nihon Emulsion), Alkamuls® EL 719 (Rhone-Poulenc)	13
PEG-50 castor oil	Emalex C-50 (Nihon Emulsion)	14
PEG-56 castor oil	Eumulgin® PRT 56 (Pulcra SA)	>10
PEG-60 castor oil	Nikkol CO-60TX (Nikko)	14
PEG-100 castor oil	Thornley	>10
PEG-200 castor oil	Eumulgin® PRT 200 (Pulcra SA)	>10
PEG-5 hydrogenated castor oil	Nikkol HCO-5 (Nikko)	6
PEG-7 hydrogenated castor oil	Simusol® 989 (Seppic), Cremophor WO7 (BASF)	6
PEG-10 hydrogenated castor oil	Nikkol HCO-10 (Nikko)	6.5
PEG-20 hydrogenated castor oil	Nikkol HCO-20 (Nikko)	11
PEG-25 hydrogenated castor oil	Simulsol® 1292 (Seppic), Cerex ELS 250 (Auschem SpA)	11
PEG-30 hydrogenated castor oil	Nikkol HCO-30 (Nikko)	11
PEG-40 hydrogenated castor oil	Cremophor RH 40 (BASF), Croduret (Croda), Emulgin HRE 40 (Henkel)	13
PEG-45 hydrogenated castor oil	Cerex ELS 450 (Auschem Spa)	14
PEG-50 hydrogenated castor oil	Emalex HC-50 (Nihon Emulsion)	14
PEG-60 hydrogenated castor oil	Nikkol HCO-60 (Nikko); Cremophor RH 60 (BASF)	15
PEG-80 hydrogenated castor oil	Nikkol HCO-80 (Nikko)	15
PEG-100 hydrogenated castor oil	Nikkol HCO -100 (Nikko)	17
PEG-6 corn oil	Labrafil® M 2125 CS (Gattefosse)	4
PEG-6 almond oil	Labrafil® M 1966 CS (Gattefosse)	4

PEG-6 apricot kernel oil	Labrafil® M 1944 CS (Gattefosse)	4
PEG-6 olive oil	Labrafil® M 1980 CS (Gattefosse)	4
PEG-6 peanut oil	Labrafil® M 1969 CS (Gattefosse)	4
PEG-6 hydrogenated palm kernel oil	Labrafil® M 2130 BS (Gattefosse)	4
PEG-6 palm kernel oil	Labrafil® M 2130 CS (Gattefosse)	4
PEG-6 triolein	Labrafil® M 2735 CS (Gattefosse)	4
PEG-8 corn oil	Labrafil® WL 2609 BS (Gattefosse)	6-7
PEG-20 corn glycerides	Crovol M40 (Croda)	10
PEG-20 almond glycerides	Crovol A40 (Croda)	10
PEG-25 trioleate	TAGAT® TO (Goldschmidt)	11
PEG-40 palm kernel oil	Crovol PK-70	>10
PEG-60 corn glycerides	Crovol M70(Croda)	15
PEG-60 almond glycerides	Crovol A70 (Croda)	15
PEG-4 caprylic/capric triglyceride	Labrafac® Hydro (Gattefosse),	4-5
PEG-8 caprylic/capric glycerides	Labrasol (Gattefosse),Labrafac CM 10 (Gattefosse)	>10
PEG-6 caprylic/capric glycerides	SOFTIGEN® 767 (Hüls), Glycerox 767 (Croda)	19
Lauroyl macrogol-32 glyceride	GELUCIRE 44/14 (Gattefosse)	14
Stearoyl macrogol glyceride	GELUCIRE 50/13 (Gattefosse)	13
Mono, di, tri, tetra esters of vegetable oils and sorbitol	SorbitoGlyceride (Gattefosse)	<10
Pentaerythrityl tetraisostearate	Crodamol PTIS (Croda)	<10
Pentaerythrityl distearate	Albunol DS (Taiwan Surf.)	<10
Pentaerythrityl tetraoleate	Liponate PO-4 (Lipo Chem.)	<10
Pentaerythrityl tetrastearate	Liponate PS-4 (Lipo Chem.)	<10

	Pentaerythrityl tetracaprylate/tetracaprate	Liponate PE-810 (Lipo Chem.), Crodamol PTC (Croda)	<10
	Pentaerythrityl tetraoctanoate	Nikkol Pentarate 408 (Nikko)	

Also included as oils in this category of surfactants are oil-soluble vitamins, such as vitamins A, D, E, K, etc. Thus, derivatives of these vitamins, such as tocopheryl PEG-1000 succinate (TPGS, available from Eastman), are also suitable surfactants.

3.6. Polyglycerized Fatty Acids

Polyglycerol esters of fatty acids are also suitable surfactants for the present invention. Among the polyglyceryl fatty acid esters, preferred hydrophobic surfactants include polyglyceryl oleate (Plurol Oleique), polyglyceryl-2 dioleate (Nikkol DGDO), and polyglyceryl-10 trioleate. Preferred hydrophilic surfactants include polyglyceryl-10 laurate (Nikkol Decaglyn 1-L), polyglyceryl-10 oleate (Nikkol Decaglyn 1-O), and polyglyceryl-10 mono, dioleate (Caprol® PEG 860). Polyglyceryl polyricinoleates (Polymuls) are also preferred hydrophilic and hydrophobic surfactants. Examples of suitable polyglyceryl esters are shown in Table 6.

Table 6: Polyglycerized Fatty Acids

COMPOUND	COMMERCIAL PRODUCT (Supplier)	HLB
Polyglyceryl-2 stearate	Nikkol DGMS (Nikko)	5-7
Polyglyceryl-2 oleate	Nikkol DGMO (Nikko)	5-7
Polyglyceryl-2 isostearate	Nikkol DGMIS (Nikko)	5-7
Polyglyceryl-3 oleate	Caprol® 3GO (ABITEC), Drewpol 3-1-O (Stepan)	6.5
Polyglyceryl-4 oleate	Nikkol Tetraglyn 1-O (Nikko)	5-7
Polyglyceryl-4 stearate	Nikkol Tetraglyn 1-S (Nikko)	5-6
Polyglyceryl-6 oleate	Drewpol 6-1-O (Stepan), Nikkol Hexaglyn 1-O (Nikko)	9
Polyglyceryl-10 laurate	Nikkol Decaglyn 1-L (Nikko)	15
Polyglyceryl-10 oleate	Nikkol Decaglyn 1-O (Nikko)	14
Polyglyceryl-10 stearate	Nikkol Decaglyn 1-S (Nikko)	12

Polyglyceryl-6 ricinoleate	Nikkol Hexaglyn PR-15 (Nikko)	>8
Polyglyceryl-10 linoleate	Nikkol Decaglyn 1-LN (Nikko)	12
Polyglyceryl-6 pentaoleate	Nikkol Hexaglyn 5-O (Nikko)	<10
Polyglyceryl-3 dioleate	Cremophor GO32 (BASF)	<10
Polyglyceryl-3 distearate	Cremophor GS32 (BASF)	<10
Polyglyceryl-4 pentaoleate	Nikkol Tetraglyn 5-O (Nikko)	<10
Polyglyceryl-6 dioleate	Caprol® 6G20 (ABITEC); Hodag PGO-62 (Calgene), PLUROL OLEIQUE CC 497 (Gattefosse)	8.5
Polyglyceryl-2 dioleate	Nikkol DGDO (Nikko)	7
Polyglyceryl-10 trioleate	Nikkol Decaglyn 3-O (Nikko)	7
Polyglyceryl-10 pentaoleate	Nikkol Decaglyn 5-O (Nikko)	3.5
Polyglyceryl-10 septaoleate	Nikkol Decaglyn 7-O (Nikko)	3
Polyglyceryl-10 tetraoleate	Caprol® 10G4O (ABITEC); Hodag PGO-62 (CALGENE), Drewpol 10-4-O (Stepan)	6.2
Polyglyceryl-10 decaisostearate	Nikkol Decaglyn 10-IS (Nikko)	<10
Polyglyceryl-10l decaoleate	Drewpol 10-10-O (Stepan), Caprol 10G10O (ABITEC), Nikkol Decaglyn 10-O	3.5
Polyglyceryl-10 mono, dioleate	Caprol® PGE 860 (ABITEC)	11
Polyglyceryl polyricinoleate	Polymuls (Henkel)	3-20

3.7. Propylene Glycol Fatty Acid Esters

Esters of propylene glycol and fatty acids are suitable surfactants for use in the present invention. In this surfactant class, preferred hydrophobic surfactants include propylene glycol monolaurate (Lauroglycol FCC), propylene glycol ricinoleate (Propymuls), propylene glycol monooleate (Myverol P-O6), propylene glycol dicaprylate/dicaprate (Captex® 200), and propylene glycol dioctanoate (Captex® 800). Examples of surfactants of this class are given in Table 7.

Table 7: Propylene Glycol Fatty Acid Esters

COMPOUND	COMMERCIAL PRODUCT (Supplier)	HLB
Propylene glycol monocaprylate	Capryol 90 (Gattefosse), Nikkol Sefsol 218 (Nikko)	<10
Propylene glycol monolaurate	Lauroglycol 90 (Gattefosse), Lauroglycol FCC (Gattefosse)	<10
Propylene glycol oleate	Lutrol OP2000 (BASF)	<10
Propylene glycol myristate	Mirpyl	<10
Propylene glycol monostearate	ADM PGME-03 (ADM), LIPO PGMS (Lipo Chem.), Aldo® PGHMS (Lonza)	3-4
Propylene glycol hydroxy stearate		<10
Propylene glycol ricinoleate	PROPYMULS (Henkel)	<10
Propylene glycol isostearate		<10
Propylene glycol monooleate	Myverol P-O6 (Eastman)	<10
Propylene glycol dicaprylate/dicaprate	Captex® 200 (ABITEC), Miglyol® 840 (Hüls), Neobee® M-20 (Stepan)	>6
Propylene glycol dioctanoate	Captex® 800 (ABITEC)	>6
Propylene glycol caprylate/caprate	LABRAFAC PG (Gattefosse)	>6
Propylene glycol dilaurate		>6
Propylene glycol distearate	Kessco® PGDS (Stepan)	>6
Propylene glycol dicaprylate	Nikkol Sefsol 228 (Nikko)	>6
Propylene glycol dicaprate	Nikkol PDD (Nikko)	>6

3.8. Mixtures of Propylene Glycol Esters - Glycerol Esters

In general, mixtures of surfactants are also suitable for use in the present invention. In particular, mixtures of propylene glycol fatty acid esters and glycerol fatty acid esters are suitable and are commercially available. One preferred mixture is composed of the oleic acid esters of propylene glycol and glycerol (Arlacel 186). Examples of these surfactants are shown in Table 8.

Table 8: Glycerol/Propylene Glycol Fatty Acid Esters

COMPOUND	COMMERCIAL PRODUCT (Supplier)	HLB
Oleic	ATMOS 300, ARLACEL 186 (ICI)	3-4
Stearic	ATMOS 150	3-4

3.9. Mono- and Diglycerides

A particularly important class of surfactants is the class of mono- and diglycerides. These surfactants are generally hydrophobic. Preferred hydrophobic surfactants in this class of compounds include glyceryl monooleate (Peceol), glyceryl ricinoleate, glyceryl laurate, glyceryl dilaurate (Capmul® GDL), glyceryl dioleate (Capmul® GDO), glyceryl mono/dioleate (Capmul® GMO-K), glyceryl caprylate/caprate (Capmul® MCM), caprylic acid mono/diglycerides (Imwitor® 988), and mono- and diacetylated monoglycerides (Myvacet® 9-45). Examples of these surfactants are given in Table 9.

Table 9: Mono- and Diglyceride Surfactants

COMPOUND	COMMERCIAL PRODUCT (Supplier)	HLB
Monopalmitolein (C16:1)	(Larodan)	<10
Monoelaidin (C18:1)	(Larodan)	<10
Monocaproin (C6)	(Larodan)	<10
Monocaprylin	(Larodan)	<10
Monocaprin	(Larodan)	<10
Monolaurin	(Larodan)	<10
Glyceryl monomyristate (C14)	Nikkol MGM (Nikko)	3-4
Glyceryl monooleate (C18:1)	PECEOL (Gattefosse), Hodag GMO-D, Nikkol MGO (Nikko)	3-4
Glyceryl monooleate	RYLO series (Danisco), DIMODAN series (Danisco), EMULDAN (Danisco), ALDO® MO FG (Lonza), Kessco GMO (Stepan), MONOMULS® series (Henkel), TEGIN O, DREWMULSE GMO (Stepan), Atlas G-695 (ICI), GMOrphic 80 (Eastman), ADM DMG-40, 70, and 100 (ADM), Myverol (Eastman)	3-4

Glycerol monooleate/linoleate	OLICINE (Gattefosse)	3-4
Glycerol monolinoleate	Maisine (Gattefosse), MYVEROL 18-92, Myverol 18-06 (Eastman)	3-4
Glyceryl ricinoleate	Softigen® 701 (Hüls), HODAG GMR-D (Calgene), ALDO® MR (Lonza)	6
Glyceryl monolaurate	ALDO® MLD (Lonza), Hodag GML (Calgene)	6.8
Glycerol monopalmitate	Emalex GMS-P (Nihon)	4
Glycerol monostearate	Capmul® GMS (ABITEC), Myvaplex (Eastman), IMWITOR® 191 (Hüls), CUTINA GMS, Aldo® MS (Lonza), Nikkol MGS series (Nikko)	5-9
Glyceryl mono-,dioleate	Capmul® GMO-K (ABITEC)	<10
Glyceryl palmitic/stearic	CUTINA MD-A, ESTAGEL-G18	<10
Glyceryl acetate	Lamegin® EE (Grünau GmbH)	<10
Glyceryl laurate	Imwitor® 312 (Hüls), Monomuls® 90-45 (Grünau GmbH), Aldo® MLD (Lonza)	4
Glyceryl citrate/lactate/oleate/ linoleate	Imwitor® 375 (Hüls)	<10
Glyceryl caprylate	Imwitor® 308 (Hüls), Capmul® MCMC8 (ABITEC)	5-6
Glyceryl caprylate/caprate	Capmul® MCM (ABITEC)	5-6
Caprylic acid mono,diglycerides	Imwitor® 988 (Hüls)	5-6
Caprylic/capric glycerides	Imwitor® 742 (Hüls)	<10
Mono-and diacetylated monoglycerides	Myvacet® 9-45, Myvacet® 9-40, Myvacet® 9-08 (Eastman), Lamegin® (Grünau)	3.8-4
Glyceryl monostearate	Aldo® MS, Arlacel 129 (ICI), LIPO GMS (Lipo Chem.), Imwitor® 191 (Hüls), Myvaplex (Eastman)	4.4
Lactic acid esters of mono,diglycerides	LAMEGIN GLP (Henkel)	<10
Dicaproin (C6)	(Larodan)	<10

Dicaprin (C10)	(Larodan)	<10
Dioctanoin (C8)	(Larodan)	<10
Dimyristin (C14)	(Larodan)	<10
Dipalmitin (C16)	(Larodan)	<10
Distearin	(Larodan)	<10
Glyceryl dilaurate (C12)	Capmul® GDL (ABITEC)	3-4
Glyceryl dioleate	Capmul® GDO (ABITEC)	3-4
Glycerol esters of fatty acids	GELUCIRE 39/01 (Gattefosse), GELUCIRE 43/01 (Gattefosse)	1
	GELUCIRE 37/06 (Gattefosse)	6
Dipalmitolein (C16:1)	(Larodan)	<10
1,2 and 1,3-diolein (C18:1)	(Larodan)	<10
Dielaidin (C18:1)	(Larodan)	<10
Dilinolein (C18:2)	(Larodan)	<10

3.10. Sterol and Sterol Derivatives

Sterols and derivatives of sterols are suitable surfactants for use in the present invention. These surfactants can be hydrophilic or hydrophobic. Preferred derivatives include the polyethylene glycol derivatives. A preferred hydrophobic surfactant in this class is cholesterol. A preferred hydrophilic surfactant in this class is PEG-24 cholesterol ether (Solulan C-24). Examples of surfactants of this class are shown in Table 10.

Table 10: Sterol and Sterol Derivative Surfactants

COMPOUND	COMMERCIAL PRODUCT (Supplier)	HLB
Cholesterol, sitosterol, lanosterol		<10
PEG-24 cholesterol ether	Solulan C-24 (Amerchol)	>10
PEG-30 cholestanol	Nikkol DHC (Nikko)	>10

Phytosterol	GENEROL series (Henkel)	<10
PEG-25 phyto sterol	Nikkol BPSH-25 (Nikko)	>10
PEG-5 soya sterol	Nikkol BPS-5 (Nikko)	<10
PEG-10 soya sterol	Nikkol BPS-10 (Nikko)	<10
PEG-20 soya sterol	Nikkol BPS-20 (Nikko)	<10
PEG-30 soya sterol	Nikkol BPS-30 (Nikko)	>10

3.11. Polyethylene Glycol Sorbitan Fatty Acid Esters

A variety of PEG-sorbitan fatty acid esters are available and are suitable for use as surfactants in the present invention. In general, these surfactants are hydrophilic, although several hydrophobic surfactants of this class can be used. Among the PEG-sorbitan fatty acid esters, preferred hydrophilic surfactants include PEG-20 sorbitan monolaurate (Tween-20), PEG-20 sorbitan monopalmitate (Tween-40), PEG-20 sorbitan monostearate (Tween-60), and PEG-20 sorbitan monooleate (Tween-80). Examples of these surfactants are shown in Table 11.

Table 11: PEG-Sorbitan Fatty Acid Esters

COMPOUND	COMMERCIAL PRODUCT (Supplier)	HLB
PEG-10 sorbitan laurate	Liposorb L-10 (Lipo Chem.)	>10
PEG-20 sorbitan monolaurate	Tween-20 (Atlas/ICI), Crillet 1 (Croda), DACOL MLS 20 (Condea)	17
PEG-4 sorbitan monolaurate	Tween-21 (Atlas/ICI), Crillet 11 (Croda)	13
PEG-80 sorbitan monolaurate	Hodag PSML-80 (Calgene); T-Maz 28	>10
PEG-6 sorbitan monolaurate	Nikkol GL-1 (Nikko)	16
PEG-20 sorbitan monopalmitate	Tween-40 (Atlas/ICI), Crillet 2 (Croda)	16
PEG-20 sorbitan monostearate	Tween-60 (Atlas/ICI), Crillet 3 (Croda)	15
PEG-4 sorbitan monostearate	Tween-61 (Atlas/ICI), Crillet 31 (Croda)	9.6
PEG-8 sorbitan monostearate	DACOL MSS (Condea)	>10
PEG-6 sorbitan monostearate	Nikkol TS106 (Nikko)	11

PEG-20 sorbitan tristearate	Tween-65 (Atlas/ICI), Crillet 35 (Croda)	11
PEG-6 sorbitan tetrastearate	Nikkol GS-6 (Nikko)	3
PEG-60 sorbitan tetrastearate	Nikkol GS-460 (Nikko)	13
PEG-5 sorbitan monooleate	Tween-81 (Atlas/ICI), Crillet 41 (Croda)	10
PEG-6 sorbitan monooleate	Nikkol TO-106 (Nikko)	10
PEG-20 sorbitan monooleate	Tween-80 (Atlas/ICI), Crillet 4 (Croda)	15
PEG-40 sorbitan oleate	Emalex ET 8040 (Nihon Emulsion)	18
PEG-20 sorbitan trioleate	Tween-85 (Atlas/ICI), Crillet 45 (Croda)	11
PEG-6 sorbitan tetraoleate	Nikkol GO-4 (Nikko)	8.5
PEG-30 sorbitan tetraoleate	Nikkol GO-430 (Nikko)	12
PEG-40 sorbitan tetraoleate	Nikkol GO-440 (Nikko)	13
PEG-20 sorbitan monoisostearate	Tween-120 (Atlas/ICI), Crillet 6 (Croda)	>10
PEG sorbitol hexaoleate	Atlas G-1086 (ICI)	10
PEG-6 sorbitol hexastearate	Nikkol GS-6 (Nikko)	3

3.12. Polyethylene Glycol Alkyl Ethers

Ethers of polyethylene glycol and alkyl alcohols are suitable surfactants for use in the present invention. Preferred hydrophobic ethers include PEG-3 oleyl ether (Volpo 3) and PEG-4 lauryl ether (Brij 30). Examples of these surfactants are shown in Table 12.

Table 12: Polyethylene Glycol Alkyl Ethers

COMPOUND	COMMERCIAL PRODUCT (Supplier)	HLB
PEG-2 oleyl ether,oleth-2	Brij 92/93 (Atlas/ICI)	4.9
PEG-3 oleyl ether,oleth-3	Volpo 3 (Croda)	<10
PEG-5 oleyl ether,oleth-5	Volpo 5 (Croda)	<10
PEG-10 oleyl ether,oleth-10	Volpo 10 (Croda), Brij 96/97 (Atlas/ICI)	12

	PEG-20 oleyl ether,oleth-20	Volpo 20 (Croda), Brij 98/99 (Atlas/ICI)	15
	PEG-4 lauryl ether, laureth-4	Brij 30 (Atlas/ICI)	9.7
	PEG-9 lauryl ether		>10
	PEG-23 lauryl ether, laureth-23	Brij 35 (Atlas/ICI)	17
	PEG-2 cetyl ether	Brij 52 (ICI)	5.3
	PEG-10 cetyl ether	Brij 56 (ICI)	13
	PEG-20 cetyl ether	Brij 58 (ICI)	16
	PEG-2 stearyl ether	Brij 72 (ICI)	4.9
	PEG-10 stearyl ether	Brij 76 (ICI)	12
	PEG-20 stearyl ether	Brij 78 (ICI)	15
	PEG-100 stearyl ether	Brij 700 (ICI)	>10

3.13. Sugar Esters

Esters of sugars are suitable surfactants for use in the present invention. Preferred hydrophilic surfactants in this class include sucrose monopalmitate and sucrose monolaurate. Examples of such surfactants are shown in Table 13.

Table 13: Sugar Ester Surfactants

COMPOUND	COMMERCIAL PRODUCT (Supplier)	HLB
Sucrose distearate	SUCRO ESTER 7 (Gattefosse), Crodesta F-10 (Croda)	3
Sucrose distearate/monostearate	SUCRO ESTER 11 (Gattefosse), Crodesta F-110 (Croda)	12
Sucrose dipalmitate		7.4
Sucrose monostearate	Crodesta F-160 (Croda)	15
Sucrose monopalmitate	SUCRO ESTER 15 (Gattefosse)	>10
Sucrose monolaurate	Saccharose monolaurate 1695 (Mitsubishi-Kasei)	15

3.14. Polyethylene Glycol Alkyl Phenols

Several hydrophilic PEG-alkyl phenol surfactants are available, and are suitable for use in the present invention. Examples of these surfactants are shown in Table 14.

Table 14: Polyethylene Glycol Alkyl Phenol Surfactants

COMPOUND	COMMERCIAL PRODUCT (Supplier)	HLB
PEG-10-100 nonyl phenol	Triton X series (Rohm & Haas), Igepal CA series (GAF, USA), Antarox CA series (GAF, UK)	>10
PEG-15-100 octyl phenol ether	Triton N-series (Rohm & Haas), Igepal CO series (GAF, USA), Antarox CO series (GAF, UK)	>10

3.15. Polyoxyethylene-Polyoxypropylene Block Copolymers

The POE-POP block copolymers are a unique class of polymeric surfactants. The unique structure of the surfactants, with hydrophilic POE and hydrophobic POP moieties in well-defined ratios and positions, provides a wide variety of surfactants suitable for use in the present invention. These surfactants are available under various trade names, including Synperonic PE series (ICI); Pluronic® series (BASF), Emkalyx, Lutrol (BASF), Supronic, Monolan, Pluracare, and Plurodac. The generic term for these polymers is "poloxamer" (CAS 9003-11-6). These polymers have the formula:

$$HO(C_2H_4O)_a(C_3H_6O)_b(C_2H_4O)_aH$$

where "a" and "b" denote the number of polyoxyethylene and polyoxypropylene units, respectively.

Preferred hydrophilic surfactants of this class include poloxamers 108, 188, 217, 238, 288, 338, and 407. Preferred hydrophobic surfactants in this class include poloxamers 124, 182, 183, 212, 331, and 335.

Examples of suitable surfactants of this class are shown in Table 15. Since the compounds are widely available; commercial sources are not listed in the Table. The compounds are listed by generic name, with the corresponding "a" and "b" values.

Table 15: POE-POP Block Copolymers

COMPOUND	a, b values in $HO(C_2H_4O)_a(C_3H_6O)_b(C_2H_4O)_aH$	HLB
Poloxamer 105	a = 11 b = 16	8
Poloxamer 108	a = 46 b = 16	>10

Poloxamer 122	a = 5	b = 21	3
Poloxamer 123	a = 7	b = 21	7
Poloxamer 124	a = 11	b = 21	>7
Poloxamer 181	a = 3	b = 30	
Poloxamer 182	a = 8	b = 30	2
Poloxamer 183	a = 10	b = 30	
Poloxamer 184	a = 13	b = 30	
Poloxamer 185	a = 19	b = 30	
Poloxamer 188	a = 75	b = 30	29
Poloxamer 212	a = 8	b = 35	
Poloxamer 215	a = 24	b = 35	
Poloxamer 217	a = 52	b = 35	
Poloxamer 231	a = 16	b = 39	
Poloxamer 234	a = 22	b = 39	
Poloxamer 235	a = 27	b = 39	
Poloxamer 237	a = 62	b = 39	24
Poloxamer 238	a = 97	b = 39	
Poloxamer 282	a = 10	b = 47	
Poloxamer 284	a = 21	b = 47	
Poloxamer 288	a = 122	b = 47	>10
Poloxamer 331	a = 7	b = 54	0.5
Poloxamer 333	a = 20	b = 54	
Poloxamer 334	a = 31	b = 54	
Poloxamer 335	a = 38	b = 54	
Poloxamer 338	a = 128	b = 54	
Poloxamer 401	a = 6	b = 67	

Poloxamer 402	a = 13	b = 67
Poloxamer 403	a = 21	b = 67
Poloxamer 407	a = 98	b = 67

3.16. Sorbitan Fatty Acid Esters

Sorbitan esters of fatty acids are suitable surfactants for use in the present invention. Among these esters, preferred hydrophobic surfactants include sorbitan monolaurate (Arlacel 20), sorbitan monopalmitate (Span-40), sorbitan monooleate (Span-80), sorbitan monostearate, and sorbitan tristearate. Examples of these surfactants are shown in Table 16.

Table 16: Sorbitan Fatty Acid Ester Surfactants

COMPOUND	COMMERCIAL PRODUCT (Supplier)	HLB
Sorbitan monolaurate	Span-20 (Atlas/ICI), Crill 1 (Croda), Arlacel 20 (ICI)	8.6
Sorbitan monopalmitate	Span-40 (Atlas/ICI), Crill 2 (Croda), Nikkol SP-10 (Nikko)	6.7
Sorbitan monooleate	Span-80 (Atlas/ICI), Crill 4 (Croda), Crill 50 (Croda)	4.3
Sorbitan monostearate	Span-60 (Atlas/ICI), Crill 3 (Croda), Nikkol SS-10 (Nikko)	4.7
Sorbitan trioleate	Span-85 (Atlas/ICI), Crill 45 (Croda), Nikkol SO-30 (Nikko)	4.3
Sorbitan sesquioleate	Arlacel-C (ICI), Crill 43 (Croda), Nikkol SO-15 (Nikko)	3.7
Sorbitan tristearate	Span-65 (Atlas/ICI) Crill 35 (Croda), Nikkol SS-30 (Nikko)	2.1
Sorbitan monoisostearate	Crill 6 (Croda), Nikkol SI-10 (Nikko)	4.7
Sorbitan sesquistearate	Nikkol SS-15 (Nikko)	4.2

3.17. Lower Alcohol Fatty Acid Esters

Esters of lower alcohols (C_2 to C_4) and fatty acids (C_8 to C_{18}) are suitable surfactants for use in the present invention. Among these esters, preferred hydrophobic surfactants include ethyl oleate (Crodamol EO), isopropyl myristate (Crodamol IPM), and isopropyl palmitate (Crodamol IPP). Examples of these surfactants are shown in Table 17.

Table 17: Lower Alcohol Fatty Acid Ester Surfactants

COMPOUND	COMMERCIAL PRODUCT (Supplier)	HLB
Ethyl oleate	Crodamol EO (Croda), Nikkol EOO (Nikko)	<10
Isopropyl myristate	Crodamol IPM (Croda)	<10
Isopropyl palmitate	Crodamol IPP (Croda)	<10
Ethyl linoleate	Nikkol VF-E (Nikko)	<10
Isopropyl linoleate	Nikkol VF-IP (Nikko)	<10

3.18. Ionic Surfactants

Ionic surfactants, including cationic, anionic and zwitterionic surfactants, are suitable hydrophilic surfactants for use in the present invention. Preferred anionic surfactants include fatty acid salts and bile salts. Specifically, preferred ionic surfactants include sodium oleate, sodium lauryl sulfate, sodium lauryl sarcosinate, sodium dioctyl sulfosuccinate, sodium cholate, and sodium taurocholate. Examples of such surfactants are shown in Table 18. For simplicity, typical counterions are shown in the entries in the Table. It will be appreciated by one skilled in the art, however, that any bioacceptable counterion may be used. For example, although the fatty acids are shown as sodium salts, other cation counterions can also be used, such as alkali metal cations or ammonium. Unlike typical non-ionic surfactants, these ionic surfactants are generally available as pure compounds, rather than commercial (proprietary) mixtures. Because these compounds are readily available from a variety of commercial suppliers, such as Aldrich, Sigma, and the like, commercial sources are not generally listed in the Table.

Table 18: Ionic Surfactants

COMPOUND	HLB
FATTY ACID SALTS	>10
Sodium caproate	
Sodium caprylate	
Sodium caprate	
Sodium laurate	
Sodium myristate	

Sodium myristolate	
Sodium palmitate	
Sodium palmitoleate	
Sodium oleate	18
Sodium ricinoleate	
Sodium linoleate	
Sodium linolenate	
Sodium stearate	
Sodium lauryl sulfate (dodecyl)	40
Sodium tetradecyl sulfate	
Sodium lauryl sarcosinate	
Sodium dioctyl sulfosuccinate [sodium docusate (Cytec)]	
BILE SALTS	>10
Sodium cholate	
Sodium taurocholate	
Sodium glycocholate	
Sodium deoxycholate	
Sodium taurodeoxycholate	
Sodium glycodeoxycholate	
Sodium ursodeoxycholate	
Sodium chenodeoxycholate	
Sodium taurochenodeoxycholate	
Sodium glyco cheno deoxycholate	
Sodium cholylsarcosinate	
Sodium N-methyl taurocholate	
PHOSPHOLIPIDS	
Egg/Soy lecithin [Epikuron™ (Lucas Meyer), Ovothin™ (Lucas Meyer)]	
Lyso egg/soy lecithin	
Hydroxylated lecithin	
Lysophosphatidylcholine	

Cardiolipin

Sphingomyelin

Phosphatidylcholine

Phosphatidyl ethanolamine

Phosphatidic acid

Phosphatidyl glycerol

Phosphatidyl serine

PHOSPHORIC ACID ESTERS

Diethanolammonium polyoxyethylene-10 oleyl ether phosphate

Esterification products of fatty alcohols or fatty alcohol ethoxylates with phosphoric acid or anhydride

CARBOXYLATES

Ether carboxylates (by oxidation of terminal OH group of fatty alcohol ethoxylates)

Succinylated monoglycerides [LAMEGIN ZE (Henkel)]

Sodium stearyl fumarate

Stearoyl propylene glycol hydrogen succinate

Mono/diacetylated tartaric acid esters of mono- and diglycerides

Citric acid esters of mono-, diglycerides

Glyceryl-lacto esters of fatty acids (CFR ref. 172.852)

Acyl lactylates:

lactylic esters of fatty acids

calcium/sodium stearoyl-2-lactylate

calcium/sodium stearoyl lactylate

Alginate salts

Propylene glycol alginate

SULFATES AND SULFONATES

Ethoxylated alkyl sulfates

Alkyl benzene sulfones

α-olefin sulfonates

Acyl isethionates

Acyl taurates

Alkyl glyceryl ether sulfonates	
Octyl sulfosuccinate disodium	
Disodium undecylenamideo-MEA-sulfosuccinate	
CATIONIC Surfactants	>10
Hexadecyl triammonium bromide	
Decyl trimethyl ammonium bromide	
Cetyl trimethyl ammonium bromide	
Dodecyl ammonium chloride	
Alkyl benzyldimethylammonium salts	
Diisobutyl phenoxyethoxydimethyl benzylammonium salts	
Alkylpyridinium salts	
Betaines (trialkylglycine):	
Lauryl betaine (N-lauryl,N,N-dimethylglycine)	
Ethoxylated amines:	
Polyoxyethylene-15 coconut amine	

It is surprisingly found that pharmaceutical compositions of ionizable hydrophobic therapeutic agents including at least one surfactant in the carrier are capable of delivering the therapeutic agent without suffering from precipitation of the therapeutic agent in the gastrointestinal tract. In conventional formulations containing an ionizable hydrophobic therapeutic agent and an ionizing agent, the ionizing agent ionizes the therapeutic agent, enabling it to be solubilized. Upon dilution by ambient fluids in the gastrointestinal tract, and exposure to the pH conditions therein, however, such conventional formulations are prone to precipitation of the therapeutic agent. Thus, while the addition of an ionizing agent provides a dosage form of solubilized therapeutic agent, solubilization *in vivo* remains problematic. In contrast, the formulations of the present invention maintain the therapeutic agent in solubilized form by protecting the therapeutic agent with a surfactant.

Preferably, the carrier includes at least one non-ionic surfactant selected from the group consisting of alkylglucosides; alkylmaltosides; alkylthioglucosides; lauryl macrogolglycerides; polyoxyethylene alkyl ethers; polyoxyethylene alkylphenols; polyethylene glycol fatty acids esters; polyethylene glycol glycerol fatty acid esters; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene-polyoxypropylene block

copolymers; polyglyceryl fatty acid esters; polyoxyethylene glycerides; polyoxyethylene sterols, derivatives, and analogues thereof; polyoxyethylene vegetable oils; polyoxyethylene hydrogenated vegetable oils; reaction mixtures of polyols and at least one member of the group consisting of fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols; sugar esters, sugar ethers; sucroglycerides; and mixtures thereof.

More preferably, the non-ionic hydrophilic surfactant is selected from the group consisting of polyoxyethylene alkylethers; polyethylene glycol fatty acids esters; polyethylene glycol glycerol fatty acid esters; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene-polyoxypropylene block copolymers; polyglyceryl fatty acid esters; polyoxyethylene glycerides; polyoxyethylene vegetable oils; and polyoxyethylene hydrogenated vegetable oils. The glyceride can be a monoglyceride, diglyceride, triglyceride, or a mixture.

Also preferred are non-ionic hydrophilic surfactants that are reaction mixtures of polyols and fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils or sterols. These reaction mixtures are largely composed of the transesterification products of the reaction, along with often complex mixtures of other reaction products. The polyol is preferably glycerol, ethylene glycol, polyethylene glycol, sorbitol, propylene glycol, or pentaerythritol.

Several particularly preferred carrier compositions are those which include as a non-ionic hydrophilic surfactant PEG-10 laurate, PEG-12 laurate, PEG-20 laurate, PEG-32 laurate, PEG-32 dilaurate, PEG-12 oleate, PEG-15 oleate, PEG-20 oleate, PEG-20 dioleate, PEG-32 oleate, PEG-200 oleate, PEG-400 oleate, PEG-15 stearate, PEG-32 distearate, PEG-40 stearate, PEG-100 stearate, PEG-20 dilaurate, PEG-25 glyceryl trioleate, PEG-32 dioleate, PEG-20 glyceryl laurate, PEG-30 glyceryl laurate, PEG-20 glyceryl stearate, PEG-20 glyceryl oleate, PEG-30 glyceryl oleate, PEG-30 glyceryl laurate, PEG-40 glyceryl laurate, PEG-40 palm kernel oil, PEG-50 hydrogenated castor oil, PEG-40 castor oil, PEG-35 castor oil, PEG-60 castor oil, PEG-40 hydrogenated castor oil, PEG-60 hydrogenated castor oil, PEG-60 corn oil, PEG-6 caprate/caprylate glycerides, PEG-8 caprate/caprylate glycerides, polyglyceryl-10 laurate, PEG-30 cholesterol, PEG-25 phyto sterol, PEG-30 soya sterol, PEG-20 trioleate, PEG-40 sorbitan oleate, PEG-80 sorbitan laurate, polysorbate 20, polysorbate 80, POE-9 lauryl ether, POE-23 lauryl ether, POE-10 oleyl ether, POE-20 oleyl ether, POE-20 stearyl

ether, tocopheryl PEG-100 succinate, PEG-24 cholesterol, polyglyceryl-10 oleate, Tween 40, Tween 60, sucrose monostearate, sucrose monolaurate, sucrose monopalmitate, PEG 10-100 nonyl phenol series, PEG 15-100 octyl phenol series, or a poloxamer.

Among these preferred surfactants, more preferred are PEG-20 laurate, PEG-20 oleate, PEG-35 castor oil, PEG-40 palm kernel oil, PEG-40 hydrogenated castor oil, PEG-60 corn oil, PEG-25 glyceryl trioleate, polyglyceryl-10 laurate, PEG-6 caprate/caprylate glycerides, PEG-8 caprate/caprylate glycerides, PEG-30 cholesterol, polysorbate 20, polysorbate 80, POE-9 lauryl ether, POE-23 lauryl ether, POE-10 oleyl ether, PEG-24 cholesterol, sucrose monostearate, sucrose monolaurate and poloxamers. Most preferred are PEG-35 castor oil, PEG-40 hydrogenated castor oil, PEG-60 corn oil, PEG-25 glyceryl trioleate, PEG-6 caprate/caprylate glycerides, PEG-8 caprate/caprylate glycerides, polysorbate 20, polysorbate 80, tocopheryl PEG-1000 succinate, PEG-24 cholesterol, and hydrophilic poloxamers.

In carrier compositions that include at least one hydrophobic surfactant, the hydrophobic surfactant is preferably a surfactant selected from the group consisting of alcohols; polyoxyethylene alkylethers; fatty acids; glycerol fatty acid esters; acetylated glycerol fatty acid esters; lower alcohol fatty acids esters; polyethylene glycol fatty acids esters; polyethylene glycol glycerol fatty acid esters; polypropylene glycol fatty acid esters; polyoxyethylene glycerides; lactic acid derivatives of mono/diglycerides; propylene glycol diglycerides; sorbitan fatty acid esters; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene-polyoxypropylene block copolymers; transesterified vegetable oils; sterols; sterol derivatives; sugar esters; sugar ethers; sucroglycerides; polyoxyethylene vegetable oils; and polyoxyethylene hydrogenated vegetable oils.

As with the hydrophilic surfactants, hydrophobic surfactants can be reaction mixtures of polyols and fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols.

Preferably, the hydrophobic surfactant is selected from the group consisting of fatty acids; lower alcohol fatty acid esters; polyethylene glycol glycerol fatty acid esters; polypropylene glycol fatty acid esters; polyoxyethylene glycerides; glycerol fatty acid esters; acetylated glycerol fatty acid esters; lactic acid derivatives of mono/diglycerides; sorbitan fatty acid esters; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene-polyoxypropylene block copolymers; polyoxyethylene vegetable oils; polyoxyethylene

hydrogenated vegetable oils; and reaction mixtures of polyols and fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols.

More preferred are lower alcohol fatty acids esters; polypropylene glycol fatty acid esters; propylene glycol fatty acid esters; glycerol fatty acid esters; acetylated glycerol fatty acid esters; lactic acid derivatives of mono/diglycerides; sorbitan fatty acid esters; polyoxyethylene vegetable oils; and mixtures thereof, with glycerol fatty acid esters and acetylated glycerol fatty acid esters being most preferred. Among the glycerol fatty acid esters, the esters are preferably mono- or diglycerides, or mixtures of mono- and diglycerides, where the fatty acid moiety is a C_6 to C_{20} fatty acid.

Also preferred are hydrophobic surfactants which are the reaction mixture of polyols and fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols. Preferred polyols are polyethylene glycol, sorbitol, propylene glycol, and pentaerythritol.

Specifically preferred hydrophobic surfactants include myristic acid; oleic acid; lauric acid; stearic acid; palmitic acid; PEG 1-4 stearate; PEG 2-4 oleate; PEG-4 dilaurate; PEG-4 dioleate; PEG-4 distearate; PEG-6 dioleate; PEG-6 distearate; PEG-8 dioleate; PEG 3-16 castor oil; PEG 5-10 hydrogenated castor oil; PEG 6-20 corn oil; PEG 6-20 almond oil; PEG-6 olive oil; PEG-6 peanut oil; PEG-6 palm kernel oil; PEG-6 hydrogenated palm kernel oil; PEG-4 capric/caprylic triglyceride, mono, di, tri, tetra esters of vegetable oil and sorbitol; pentaerythrityl di, tetra stearate, isostearate, oleate, caprylate, or caprate; polyglyceryl 2-4 oleate, stearate, or isostearate; polyglyceryl 4-10 pentaoleate; polyglyceryl-3 dioleate; polyglyceryl-6 dioleate; polyglyceryl-10 trioleate; polyglyceryl-3 distearate; propylene glycol mono- or diesters of a C_6 to C_{20} fatty acid; monoglycerides of C_6 to C_{20} fatty acids; acetylated monoglycerides of C_6 to C_{20} fatty acids; diglycerides of C_6 to C_{20} fatty acids; lactic acid derivatives of monoglycerides; lactic acid derivatives of diglycerides; cholesterol; phytosterol; PEG 5-20 soya sterol; PEG-6 sorbitan tetra, hexastearate; PEG-6 sorbitan tetraoleate; sorbitan monolaurate; sorbitan monopalmitate; sorbitan mono, trioleate; sorbitan mono, tristearate; sorbitan monoisostearate; sorbitan sesquioleate; sorbitan sesquistearate; PEG 2-5 oleyl ether; POE 2-4 lauryl ether; PEG-2 cetyl ether; PEG-2 stearyl ether; sucrose distearate; sucrose dipalmitate; ethyl oleate; isopropyl myristate; isopropyl palmitate; ethyl linoleate; isopropyl linoleate; and poloxamers.

Among the specifically preferred hydrophobic surfactants, most preferred are oleic acid; lauric acid; glyceryl monocaprate; glyceryl monocaprylate; glyceryl monolaurate; glyceryl monooleate; glyceryl dicaprate; glyceryl dicaprylate; glyceryl dilaurate; glyceryl dioleate; acetylated monoglycerides; propylene glycol oleate; propylene glycol laurate; polyglyceryl-3 oleate; polyglyceryl-6 dioleate; PEG-6 corn oil; PEG-20 corn oil; PEG-20 almond oil; sorbitan monooleate; sorbitan monolaurate; POE-4 lauryl ether; POE-3 oleyl ether; ethyl oleate; and poloxamers.

Also preferred are mixtures of at least one hydrophilic surfactant and at least one hydrophobic surfactant.

The surfactant or surfactant mixture is present in an amount sufficient to promote the continued solubilization of the therapeutic agent in the gastrointestinal tract. Although small amounts of surfactant may provide some stabilization of the solubilized therapeutic agent, it is presently preferred to include a surfactant in an amount of at least about 10%, preferably about 20-90% by weight, based on the total weight of the composition. Also preferred are mixtures of surfactants, wherein the total amount of surfactant is at least about 10%, and preferably about 20-90% by weight, based on the total weight of the composition.

4. Solubilizers

The carrier optionally includes one or more pharmaceutically acceptable solubilizers to enhance the solubility of the ionizable hydrophobic therapeutic agent in the carrier system. Examples of such compounds include:

alcohols and polyols, such as ethanol, isopropanol, butanol, benzyl alcohol, ethylene glycol, propylene glycol, butanediols and isomers thereof, glycerol, pentaerythritol, sorbitol, mannitol, dimethyl isosorbide, polyethylene glycol, polypropylene glycol, polyvinylalcohol, hydroxypropyl methylcellulose and other cellulose derivatives, maltodextrins, cyclodextrins and derivatives thereof;

ethers of polyethylene glycols having an average molecular weight of about 200 to about 6000, such as tetrahydrofurfuryl alcohol PEG ether (glycofurol, available commercially from BASF under the trade name Tetraglycol) or methoxy PEG (Union Carbide);

amides, such as 2-pyrrolidone, 2-piperidone, ε-caprolactam, N-alkylpyrrolidone, N-hydroxyalkylpyrrolidone, N-alkylpiperidone, N-alkylcaprolactam, dimethylacetamide, and polyvinylpyrrolidone;

esters, such as ethyl propionate, tributylcitrate, acetyl triethylcitrate, acetyl tributyl citrate, triethylcitrate, ethyl oleate, ethyl caprylate, ethyl butyrate, triacetin, propylene glycol monoacetate, propylene glycol diacetate, ε-caprolactone and isomers thereof, δ-valerolactone and isomers thereof, β-butyrolactone and isomers thereof;

and other solubilizers known in the art, such as dimethyl acetamide, dimethyl isosorbide (Arlasolve DMI (ICI)), N-methyl pyrrolidones (Pharmasolve (ISP)), transcutol, monooctanoin, and water.

Mixtures of solubilizers are also within the scope of the invention. Except as indicated, these compounds are readily available from standard commercial sources.

Preferred solubilizers include ethanol, isopropanol, butanol, benzyl alcohol, ethylene glycol, propylene glycol, butanediol and isomers thereof, glycerol, pentaerythritol, sorbitol, mannitol, dimethyl isosorbide, polyethylene glycol, polypropylene glycol, polyvinylalcohol, hydroxypropyl methylcellulose and other cellulose derivatives, maltodextrins, cyclodextrins and derivatives thereof, ethyl propionate, tributylcitrate, acetyl triethylcitrate, acetyl tributyl citrate, triethylcitrate, ethyl oleate, ethyl caprylate, ethyl butyrate, triacetin, propylene glycol diacetate, ε-caprolactone and isomers thereof, δ-valerolactone and isomers thereof, β-butyrolactone and isomers thereof, 2-pyrrolidone, 2-piperidone, ε-caprolactam, N-methylpyrrolidone, N-ethylpyrrolidone, N-hydroxyethyl pyrrolidone, N-octylpyrrolidone, N-laurylpyrrolidone, dimethylacetamide, polyvinylpyrrolidone, glycofurol, methoxy PEG, and mixtures thereof.

More preferred solubilizers are ethanol, isopropanol, benzyl alcohol, ethylene glycol, propylene glycol, 1,3-butanediol, glycerol, pentaerythritol, sorbitol, glycofurol, dimethyl isosorbide, polyethylene glycol, polyvinylalcohol, hydroxypropyl methylcellulose, methylcellulose, ethylcellulose, hydroxypropylcyclodextrins, sulfobutyl ether derivatives of cyclodextrins, ethyl propionate, tributylcitrate, triethylcitrate, ethyl oleate, ethyl caprylate, triacetin, β-butyrolactone and isomers thereof, 2-pyrrolidone, N-methylpyrrolidone, N-ethylpyrrolidone, N-hydroxyethylpyrrolidone, N-octylpyrrolidone, N-laurylpyrrolidone, dimethylacetamide, polyvinylpyrrolidone, and mixtures thereof.

Still more preferred are triacetin, triethylcitrate, ethyl oleate, ethyl caprylate, dimethylacetamide, N-methylpyrrolidone, N-hydroxyethylpyrrolidone, polyvinylpyrrolidone, hydroxypropyl methylcellulose, hydroxypropyl cyclodextrins,

ethanol, polyethylene glycol 200-600, glycofurol, propylene glycol, and dimethyl isosorbide. Most preferred solubilizers include sorbitol, glycerol, triacetin, ethyl alcohol, PEG-400, glycofurol and propylene glycol.

The amount of solubilizer that can be included in compositions of the present invention is not particularly limited. Of course, when such compositions are ultimately administered to a patient, the amount of a given solubilizer is limited to a bioacceptable amount. In some circumstances, it may be advantageous to include amounts of solubilizers far in excess of bioacceptable amounts in order to maximize the concentration of ionizable hydrophobic therapeutic agent, with excess solubilizer removed prior to providing the composition to a patient using conventional techniques, such as distillation or evaporation.

In a particular embodiment, the solubilizer includes at least one compound selected from the group consisting of alcohols, polyols, amides, esters, and propylene glycol ethers, the alcohol or polyol being selected from the group consisting of ethanol, isopropanol, butanol, benzyl alcohol, ethylene glycol, propylene glycol, butanediols and isomers thereof, glycerol, pentaerythritol, sorbitol, mannitol, dimethyl isosorbide, polypropylene glycol, polyvinylalcohol, hydroxypropyl methylcellulose and other cellulose derivatives, maltodextrins, and cyclodextrins and cyclodextrin derivatives. In this embodiment, the surfactant includes at least one compound selected from the group consisting of alkylglucosides; alkylmaltosides; alkylthioglucosides; lauryl macrogolglycerides; polyoxyethylene alkyl ethers; fatty acids; lower alcohol fatty acid esters; polyoxyethylene alkylphenols; polyethylene glycol fatty acids esters; polypropylene glycol fatty acid esters; glycerol fatty acid esters; acetylated glycerol fatty acid esters; polyethylene glycol glycerol fatty acid esters; polyglyceryl fatty acid esters; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene glycerides; polyoxyethylene sterols, derivatives, and analogues thereof; polyoxyethylene vegetable oils; polyoxyethylene hydrogenated vegetable oils; reaction mixtures of polyols and at least one member of the group consisting of fatty acids, vegetable oils, hydrogenated vegetable oils, and sterols; sugar esters; sugar ethers; sucroglycerides; fatty acid salts; bile salts; phospholipids; phosphoric acid esters; carboxylates; sulfates; and sulfonates.

In another particular embodiment, the solubilizer is present in an amount of greater than about 10% by weight, based on the total weight of the composition. In this embodiment, the surfactant includes at least one compound from the group consisting of

alkylglucosides; alkylmaltosides; alkylthioglucosides; lauryl macrogolglycerides; fatty acids; lower alcohol fatty acid esters; polyoxyethylene alkylphenols; polyethylene glycol fatty acid esters; polypropylene glycol fatty acid esters; glycerol fatty acid esters; acetylated glycerol fatty acid esters; polyethylene glycol glycerol fatty acid esters; polyglyceryl fatty acid esters; polyoxyethylene glycerides; polyoxyethylene sterols, derivatives, and analogues thereof; polyoxyethylene vegetable oils; polyoxyethylene hydrogenated vegetable oils; reaction mixtures of polyols and at least one member of the group consisting of fatty acids, vegetable oils, hydrogenated vegetable oils, and sterols; sugar esters, sugar ethers; sucroglycerides; fatty acid salts; bile salts; phospholipids; phosphoric acid esters; carboxylates; sulfates; and sulfonates.

5. **Triglycerides**

The carrier may also include one or more pharmaceutically acceptable triglycerides to enhance the solubility of the ionizable hydrophobic therapeutic agent in the carrier system. Examples of triglycerides suitable for use in the present invention are shown in Table 19.

Table 19: Triglycerides

Triglyceride	Commercial Source
Almond oil	Super Refined Almond Oil (Croda)
Canola oil	Lipex 108 (Abitec)
Castor oil	
Coconut oil	Pureco 76 (Abitec)
Corn oil	Super Refined Corn Oil (Croda)
Cottonseed oil	Super Refined Cottonseed Oil (Croda)
Menhaden oil	Super Refined Menhaden Oil (Croda)
Olive oil	Super Refined Olive Oil (Croda)
Peanut oil	Super Refined Peanut Oil (Croda)
Safflower oil	Super Refined Safflower Oil (Croda)
Sesame oil	Super Refined Sesame Oil (Croda)

Shark liver oil	Super Refined Shark Liver Oil (Croda)
Soybean oil	Super Refined Soybean Oil (Croda)
Wheat germ oil	Super Refined Wheat Germ Oil (Croda)
Hydrogenated castor oil	Castorwax
Hydrogenated cottonseed oil	Dritex C (Abitec)
Hydrogenated palm oil	Dritex PST (Abitec); Softisan 154 (Hüls)
Hydrogenated soybean oil	Sterotex HM NF (Abitec); Dritex S (Abitec)
Hydrogenated vegetable oil	Sterotex NF (Abitec); Hydrokote M (Abitec)
Hydrogenated cottonseed and castor oil	Sterotex K (Abitec)
Partially hydrogenated soybean oil	Hydrokote AP5 (Abitec)
Partially soy and cottonseed oil	Apex B (Abitec)
Glyceryl tributyrate	(Sigma)
Glyceryl tricaproate	(Sigma)
Glyceryl tricaprylate	(Sigma)
Glyceryl tricaprate	Captex 1000 (Abitec)
Glyceryl triundecanoate	Captex 8227 (Abitec)
Glyceryl trilaurate	(Sigma)
Glyceryl trimyristate	Dynasan 114 (Hüls)
Glyceryl tripalmitate	Dynasan 116 (Hüls)
Glyceryl tristearate	Dynasan 118 (Hüls)
Glyceryl triarchidate	(Sigma)
Glyceryl trimyristoleate	(Sigma)
Glyceryl tripalmitoleate	(Sigma)
Glyceryl trioleate	(Sigma)
Glyceryl trilinoleate	(Sigma)

Glyceryl trilinolenate	(Sigma)
Glyceryl tricaprylate/caprate	Captex 300 (Abitec); Captex 355 (Abitec); Miglyol 810 (Hüls); Miglyol 812 (Hüls)
Glyceryl tricaprylate/caprate/laurate	Captex 350 (Abitec)
Glyceryl tricaprylate/caprate/linoleate	Captex 810 (Abitec); Miglyol 818 (Hüls)
Glyceryl tricaprylate/caprate/stearate	Softisan 378 (Hüls); (Larodan)
Glyceryl tricaprylate/laurate/stearate	(Larodan)
Glyceryl 1,2-caprylate-3-linoleate	(Larodan)
Glyceryl 1,2-caprate-3-stearate	(Larodan)
Glyceryl 1,2-laurate-3-myristate	(Larodan)
Glyceryl 1,2-myristate-3-laurate	(Larodan)
Glyceryl 1,3-palmitate-2-butyrate	(Larodan)
Glyceryl 1,3-stearate-2-caprate	(Larodan)
Glyceryl 1,2-linoleate-3-caprylate	(Larodan)

Mixtures of triglycerides are also within the scope of the invention.

Preferred triglycerides include vegetable oils, fish oils, animal fats, hydrogenated vegetable oils, partially hydrogenated vegetable oils, medium and long-chain triglycerides, and structured triglycerides.

6. **Other Additives**

Other additives conventionally used in pharmaceutical compositions can be included, and these additives are well known in the art. Such additives include antioxidants, preservatives, chelating agents, complexing agents, viscomodulators, tonicifiers, flavorants, colorants odorants, opacifiers, suspending agents, binders, and mixtures thereof. The amounts of such additives can be readily determined by one skilled in the art, according to the particular properties desired.

7. **Dosage Forms**

The pharmaceutical compositions of the present invention can be provided in the form of a solution preconcentrate; *i.e.*, a composition as described above, and intended to

be dispersed with water, either prior to administration, in the form of a drink, or dispersed in vivo. Alternatively, the compositions can be provided in the form of a diluted preconcentrate (*i.e.*, an aqueous dispersion), a semi-solid dispersion or a solid dispersion. If desired, the compositions may be encapsulated in a hard or soft gelatin capsule, a starch capsule or an enteric coated capsule. The term "enteric coated capsule" as used herein means a capsule coated with a coating resistant to acid; *i.e.*, an acid resistant enteric coating.

Although formulations specifically suited to oral administration are presently preferred, the compositions of the present invention can also be formulated for topical, transdermal, ocular, pulmonary, vaginal, rectal, transmucosal or parenteral administration, in the form of a cream, lotion, ointment, suppository, gel or the like. If such a formulation is desired, other additives may be included, such as are well-known in the art, to impart the desired consistency and other properties to the formulation. The compositions of the present invention can also be formulated as a spray or an aerosol. In particular, the compositions may be formulated as a sprayable solution, and such formulation is particularly useful for spraying to coat a multiparticulate carrier, such as a bead. Such multiparticulate carriers are well known in the art.

8. **Preparation of Pharmaceutical Compositions**

The pharmaceutical compositions of the present invention can be prepared by conventional methods well known to those skilled in the art. Of course, the specific method of preparation will depend upon the ultimate dosage form. For dosage forms substantially free of water, *i.e.*, when the composition is provided in a pre-concentrated form for later dispersion in an aqueous system, the composition is prepared by simple mixing of the components to form a pre-concentrate. The mixing process can be aided by gentle heating, if desired. For compositions in the form of an aqueous dispersion, the pre-concentrate form is prepared, then the appropriate amount of purified water is added and the solution gently mixed. If any water-soluble additives are included, these may be added first as part of the pre-concentrate, or added later to the aqueous dispersion, as desired. As noted above, the hydrophobic therapeutic agent can be present in a first amount solubilized by the carrier, and a second amount suspended (not solubilized) in the carrier, as desired. It should be emphasized that the order of addition of the various components is not generally important and may be changed as convenient.

In another aspect, the present invention relates to a novel method of preparing a pharmaceutical composition of an ionizable hydrophobic therapeutic agent. The method includes the steps of: (I) providing a pharmaceutical composition having an ionizable hydrophobic therapeutic agent and a carrier which includes an ionizing agent and a surfactant; and (II) providing a neutralizing agent to neutralize at least a portion of the ionizing agent.

The pharmaceutical composition provided in step (I) can be any of the pharmaceutical compositions described herein. Preferably, the composition has greater than about 1.5 mole equivalents of ionizing agent per mole of ionizable functional group, although this concentration is not required.

The neutralizing agent provided in step (II) can be any of the pharmaceutically acceptable acids or bases described above. Of course, if the ionizing agent is an acid, the neutralizing agent is a base, and vice versa. Any amount of neutralizing agent that neutralizes at least a portion of the ionizing agent can be used. Preferably, the amount of neutralizing agent used is an amount sufficient to neutralize the ionizing agent so that the amount of ionizing agent is about 0.1 to about 1.5 mole equivalents per mole of ionizable functional group, based on the amounts of ionizing agent and ionizable functional groups present before reaction with each other, but after reaction of the ionizing agent and the neutralizing agent. More preferably, the neutralizing agent is used in an amount sufficient to neutralize the ionizing agent so that the amount of ionizing agent is about 0.1 to about 1.0 mole equivalents per mole of ionizable functional group.

For some applications, particularly for preparing pharmaceutical compositions in a gelatin capsule dosage form, it may be desirable to use a smaller amount of ionizing agent, in the range of about 0.1 to about 1.5 mole equivalents, preferably about 0.1 to about 1.0 mole equivalents, per mole of ionizable functional group, based on pre-reaction amounts. This lower amount of ionizing agent provides better compatibility with the gelatin capsule dosage form. However, as discussed above, it is desirable to use an excess of ionizing agent to promote increased solubilization and ease of preparation of solubilized compositions. Thus, in the present method, an excess of ionizing agent can be used in preparing a composition, and a portion of the excess can then be neutralized to provide a composition more suited to certain dosage forms, particularly gelatin capsule dosage forms.

The amount of neutralizing agent used is defined in such a way as to make the relative amounts of ionizing agent and ionizable functional groups in the present method consistent with the description above. Thus, it is convenient to define the amount of ionizing agent as the pre-reaction amount, before the acid-base reaction with the ionizable functional groups, as described above. In order to keep this convention, the amount of neutralizing agent is defined by adopting the following convenient fiction: first, the neutralizing agent is imagined to react with the ionizing agent, to neutralize a portion of the ionizing agent; then, the remaining ionizing agent is imagined to react with the ionizable functional groups, to ionize at least a portion of the ionizable functional groups. Thus, in a preferred embodiment, the amount of neutralizing agent is selected so that after the first step of the hypothetical two-step ionization--*i.e.*, the neutralization reaction between the neutralizing agent and the ionizing agent-- the amount of ionizing agent available in the second step is about 0.1 to about 1.5 mole equivalents, preferably about 0.1 to about 1.0 mole equivalents, per mole of ionizable functional group.

As a specific example, if the amount of ionizable functional groups is 1.0 mole, and the amount of ionizing agent used is 10.0 moles, then to achieve a concentration of ionizing agent within a pre-reaction range of 0.1 to 1.5 moles, an amount of neutralizing agent sufficient to neutralize from 8.5 to 9.9 moles of ionizing agent is used. In the hypothetical first neutralization step, the 8.5 to 9.9 mole equivalents of neutralizing agent neutralizes 8.5 to 9.9 moles of the ionization agent, leaving 0.1 to 1.5 moles unreacted. Thus, the amount of ionizing agent hypothetically present before reaction with the ionizable functional group is 0.1 to 1.5 moles. It should be apparent that the actual reaction sequence does not follow this hypothetical scheme, but such a scheme merely provides a simple stoichiometric reference frame.

9. **Methods of Treating an Animal**

In another aspect, the present invention relates to methods of improving delivery of ionizable hydrophobic therapeutic agents in an animal by administering to the animal a dosage form of the pharmaceutical compositions described herein. Preferably the animal is a mammal, and more preferably, a human. It is believed that the pharmaceutical compositions of the present invention when administered to an animal enable the ionizable hydrophobic therapeutic agent contained therein to be delivered to the absorption site with less or no precipitation of the therapeutic agent, resulting in better bioavailability.

In use, the methods and compositions of the present invention provide a number of important advantages, including:

Robustness to Dilution: The compositions of the present invention are unexpectedly robust to dilution in media simulating the conditions normally encountered in the gastrointestinal and intestinal tracts. Precipitation of the therapeutic agent is minimal, and is delayed upon administration, due to the protective effects of the surfactant and optional solubilizer components.

Improved Delivery: The compositions of the present invention unexpectedly provide improved delivery of the therapeutic agent to the absorption site, by minimizing precipitation. This improved delivery is believed to result in better bioavailability of the therapeutic agent.

Less Dependence Upon Other Factors: The compositions of the present invention enable the absorption of the hydrophobic therapeutic agent independent of wetting/dissolution rates, and less dependent upon meal, gastro-intestinal contents, and bilary secretions, by maintaining the therapeutic agent in solubilized form upon administration. In addition, when the optional triglyceride component is absent, dependence upon the rate of lipolysis is reduced or eliminated.

High Loading Capacity: The compositions of the present invention provide high loading capacity for ionizable hydrophobic therapeutic agents. The surfactants and optional triglycerides and solubilizers interact with the hydrophobic therapeutic agent to unexpectedly solubilize large amounts of therapeutic agent. In addition, when an additional non-solubilized amount of therapeutic agent is included, still larger therapeutic agent concentrations can be achieved, while still preserving the advantages in stability and bioavailability of the solubilized therapeutic agent.

Ease of Preparation: The methods of the present invention provide compositions in which the hydrophobic therapeutic agent is readily solubilized, thereby conserving expensive manufacturing and personnel resources.

Versatility: Because the compositions of the present invention can effectively make use of a wide variety of different surfactants, solubilizers and triglycerides to solubilize a wide variety of ionizable hydrophobic therapeutic agents, compositions can be carefully tailored to the polarity and functionality of the therapeutic agents, without compromising the improved solubilization, delivery, and other advantages as described above.

These and other advantages of the present invention, as well as aspects of preferred embodiments, are illustrated more fully in the Examples which follow.

EXAMPLES

Example 1: Carrier Formulations

Carrier formulations can be prepared by simple mixing of the desired components, with gentle heating if desired. Table 20 contains examples of carrier formulations according to the present invention, using a wide variety of surfactants, surfactant mixtures, solubilizers, and other components. The desired amount of ionizable hydrophobic therapeutic agent is included in the carrier to produce a pharmaceutical composition.

Table 20: Carrier Formulations

Formulation #	Composition (g)	
1	Concentrated Hydrochloric Acid	0.005
	Cremophor RH-40	0.650
	Span 80	0.300
	Sterotex NF	0.050
2	Concentrated Hydrochloric Acid	0.010
	Solulan C-24	0.700
	Crovol M-40	0.250
	Soybean Oil USP	0.050
3	Methanesulfonic Acid	0.020
	Incrocas 35	0.750
	ARLACEL 186	0.150
	Captex 300	0.100
4	Methanesulfonic Acid	0.020
	Crovol M-70	0.800
	Imwitor 988	0.200

1	5	Concentrated Hydrochloric Acid	0.015
		Incrocas 35	0.600
		Myvacet 9-45	0.400
5	6	Concentrated Phosphoric Acid	0.050
		Poloxamer 188	0.850
		Labrafil M2125CS	0.150
	7	Concentrated Phosphoric Acid	0.030
10		Cremophor EL-P	0.830
		Peceol	0.170
	8	Citric Acid (aq.)	0.050
		Crodet O40	0.680
15		Plurol Oleique	0.320
	9	Glacial Acetic Acid	0.100
		Tween 80	0.750
		Lauroglycol FCC	0.150
20	10	Glacial Acetic Acid	0.050
		Brij 35	0.750
		Labrasol	0.200
25	11	Concentrated Hydrochloric Acid	0.010
		Cremophor EL	0.300
		Labrasol	0.300
		Capmul MCM	0.400

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12	Concentrated Hydrochloric Acid	0.020
	Tween 20	0.660
	ARLACEL 186	0.170
	Sodium Taurocholate	0.170
13	Concentrated Hydrochloric Acid	0.005
	Cremophor RH-40	0.500
	Captex 200	0.200
	Captex 810	0.100
	PEG 200	0.200
14	Concentrated Hydrochloric Acid	0.010
	Cremophor RH-40	0.600
	Crovol M-40	0.200
	Hydrokote AP5	0.050
	Ethanol	0.150
15	Methanesulfonic Acid	0.020
	Incrocas 35	0.650
	ARLACEL 186	0.120
	PEG 400	0.230
16	Methanesulfonic Acid	0.020
	Crovol M-70	0.650
	Imwitor 988	0.150
	Polyethylene Glycol	0.200
17	Concentrated Hydrochloric Acid	0.015
	Incrocas 35	0.500
	Myvacet 9-45	0.350
	Methoxy PEG 400	0.150

18	Concentrated Phosphoric Acid	0.050
	Crovol M-70	0.750
	Labrafil M2125CS	0.130
	Triacetin	0.120
19	Concentrated Phosphoric Acid	0.030
	Cremophor EL-P	0.750
	Peceol	0.150
	Dimethyl Isosorbide	0.100
20	Concentrated Phosphoric Acid	0.050
	Tween 20	0.580
	Plurol Oleique	0.210
	Transcutol	0.210
21	Concentrated Phosphoric Acid	0.050
	Tween 80	0.670
	Lauroglycol FCC	0.170
	Glycofurol	0.160
22	Concentrated Phosphoric Acid	0.050
	Tween-20	0.300
	ARLACEL 186	0.150
	Propylene Glycol	0.500
23	Concentrated Hydrochloric Acid	0.020
	Cremophor RH-40	0.450
	ARLACEL 186	0.100
	Sodium Taurocholate	0.300
	Ethanol	0.150

24	Concentrated Hydrochloric Acid	0.020
	Cremophor RH-40	0.650
	ARLACEL 186	0.150
	Sodium Dodecyl Sulfate	0.100
	PEG 400	0.100
25	Concentrated Hydrochloric Acid	0.010
	Tagat L2	0.450
	Crovol A-40	0.250
	Sodium Docusate	0.150
	2-pyrrolidone	0.150
26	Concentrated Hydrochloric Acid	0.010
	Poloxamer 108	0.450
	Span 80	0.250
	Sodium Docusate	0.150
	Ethyl Oleate	0.150
27	Concentrated Phosphoric Acid	0.025
	Tween-20	0.300
	ARLACEL 186	0.200
	Sodium Taurocholeate	0.150
	Propylene Glycol	0.300
28	Concentrated Hydrochloric Acid	0.025
	Tween-20	0.300
	ARLACEL 186	0.175
	Sodium Taurocholate	0.150
	Propylene Glycol	0.300

	29	Concentrated Hydrochloric Acid	0.025
		Tween-20	0.300
		ARLACEL 186	0.150
		Sodium Taurocholate	0.150
		Propylene Glycol	0.325
	30	Concentrated Phosphoric Acid	0.100
		Tween-20	0.300
		Sodium Taurocholate	0.100
		Glycofurol	0.500
		Ethanol	0.100
	31	Concentrated Phosphoric Acid	0.100
		Tween-20	0.300
		ARLACEL 186	0.050
		Sodium Taurocholate	0.100
		Glycofurol	0.500
		Ethanol	0.100
	32	Concentrated Hydrochloric Acid	0.025
		Incrocas 40	0.500
		Crovol M-40	0.100
		Captex 355	0.100
		PEG 400	0.250
		Sodium Hydroxide (5N aq.)	0.020
	33	Methanesulfonic Acid	0.020
		Incrocas 35	0.830
		Imwitor 742	0.170
		Sodium Hydroxide (5N aq.)	0.010

	34	Methanesulfonic Acid	0.020
		Crovol M-70	0.800
		Imwitor 988	0.200
		Potassium Hydroxide (5N aq.)	0.010
	35	Concentrated Hydrochloric Acid	0.025
		Crodesta F-160	0.550
		Myvacet 9-45	0.350
		Methoxy PEG 400	0.100
		Triethylamine	0.005
	36	Concentrated Phosphoric Acid	0.050
		Poloxamer 188	0.750
		Labrafil M2125CS	0.150
		Glycofurol	0.100
		Concentrated Ammonium Hydroxide	0.010
	37	Concentrated Phosphoric Acid	0.030
		Cremophor EL-P	0.830
		Peceol	0.170
		Concentrated Sodium Acetate (aq.)	0.010
	38	Sodium Hydroxide (5N aq.)	0.010
		Crovol M-70	0.650
		Labrafil M2125CS	0.250
		Softisan 378	0.100
	39	Sodium Hydroxide (5N aq.)	0.010
		Incrocas 40	0.800
		ARLACEL 186	0.150
		Corn Oil NF	0.050

1	40	Sodium Hydroxide (5N aq.)	0.005
		Tagat TO	0.650
		Imwitor 988	0.250
		Miglyol 810	0.100
5			
	41	Sodium Hydroxide (10N aq.)	0.010
		Cremophor RH-40	0.700
		Volpo 3	0.300
10	42	Sodium Hydroxide (10N aq.)	0.005
		Cremophor EL-P	0.200
		Labrasol	0.400
		Nikkol Decaglyn 3-O	0.400
15	43	Concentrated Sodium Acetate (aq.)	0.030
		Poloxamer 108	0.850
		Capmul GMO-K	0.150
	44	Sodium Hydroxide (10N aq.)	0.008
20		Glycerox L	0.730
		Myvacet 9-45	0.270
	45	Sodium Hydroxide (10N aq.)	0.008
		Tagat L2	0.680
25		Brij 30	0.320
	46	Potassium Hydroxide (5N aq.)	0.020
		Tween 20	0.750
		Drewpol 6-1-O	0.150

30

1	47	Potassium Hydroxide (5N aq.)	0.020
		Tween 80	0.750
		Maisine 35-I	0.200
5	48	Potassium Hydroxide (5N aq.)	0.010
		Kessco PEG 1000 ML	0.300
		Labrasol	0.300
		Span 20	0.400
10	49	Potassium Hydroxide (5N aq.)	0.010
		Kessco PEG 1000 MO	0.660
		Plurol Oleique	0.170
		Sodium Taurocholate	0.170
15	50	Potassium Hydroxide (10N aq.)	0.010
		Myrj 51	0.540
		Kessco PEG 300 DL	0.200
		Corn oil NF	0.060
		PEG 200	0.200
20	51	Potassium Hydroxide (10N aq.)	0.010
		Kessco PEG 1540 DL	0.600
		Crovol A-40	0.150
		Castorwax	0.050
25		Ethanol	0.200
	52	Potassium Hydroxide (10N aq.)	0.005
		Kessco PEG 1540DO	0.650
		Span 80	0.120
30		PEG 400	0.230

1	53	Ethanolamine	0.005
		Gelucire 44/14	0.650
		Captex 200	0.150
		Polyethylene Glycol	0.200
5			
	54	Ethanolamine	0.005
		Gelucire 50/13	0.500
		Kessco PEG 300 DL	0.350
		Methoxy PEG 400	0.150
10			
	55	Triethylamine	0.005
		Nikkol Decaglyn 1-L	0.550
		Crovol M-40	0.330
		Triacetin	0.120
15			
	56	Diisopropylethylamine	0.005
		Nikkol Decaglyn 1-O	0.650
		Capmul MCM	0.250
		Dimethyl Isosorbide	0.100
20			
	57	Triethanolamine	0.005
		Solulan C-24	0.580
		Lauroglycol FCC	0.210
		Transcutol	0.210
25			
	58	Ammonium Hydroxide	0.010
		Nikkol DHC	0.670
		Nikkol TMGO-5	0.170
		Glycofurol	0.160

30

1	59	Concentrated Ammonium Acetate (aq.)	0.050
		Nikkol BPS-30	0.300
		PEG-6 Castor Oil	0.150
		Propylene Glycol	0.500
5			
	60	Concentrated Sodium Acetate (aq.)	0.050
		Cremophor RH-40	0.350
		Capmul MCM	0.300
		Sodium Taurocholate	0.200
10		Ethanol	0.100
	61	Lysine Ethyl Ester	0.010
		Poloxamer 188	0.650
		Peceol	0.150
		Sodium Dodecyl Sulfate	0.100
15		PEG 400	0.100
	62	Concentrated Sodium Citrate (aq.)	0.010
		Cremophor EL	0.450
		Crovol M-40	0.250
20		Sodium Docusate	0.150
		2-pyrrolidone	0.150
	63	Sodium Hydroxide (10N aq.)	0.010
		Softigen 767	0.450
25		Imwitor 742	0.250
		Sodium Docusate	0.150
		Ethyl Oleate	0.150

30

	64	Concentrated Potassium Phosphate (aq.)	0.025
		Poloxamer 407	0.300
		Mapeg 200 ML	0.200
		Sodium Taurocholate	0.150
		Propylene Glycol	0.300
	65	Triethylamine	0.007
		Tween-20	0.300
		ARLACEL 186	0.100
		Sodium Taurocholate	0.100
		Propylene Glycol	0.500
		Butylated Hydroxytoluene	0.010
		Edetate Disodium	0.001
	66	Sodium Hydroxide (5N aq.)	0.020
		Tween-20	0.300
		ARLACEL 186	0.100
		Sodium Taurocholate	0.100
		Propylene Glycol	0.500
		Butylated Hydroxytoluene	0.010
		Edetate Disodium	0.001
	67	Sodium Hydroxide (10N aq.)	0.020
		Tween 20	0.500
		Peceol	0.100
		Pureco 76	0.050
		PEG 400	0.300
		Concentrated Hydrochloric Acid	0.005

	68	Potassium Hydroxide (5N aq.)	0.025
		Labrasol	0.830
		Lauroglycol FCC	0.170
		Concentrated Phosphoric Acid	0.010
	69	Methanesulfonic Acid	0.020
		Crovol M-70	0.800
		Imwitor 988	0.200
		Potassium Hydroxide (5N aq.)	0.010
	70	Triethylamine	0.025
		Crovol K-70	0.550
		Captex 100	0.350
		Methoxy PEG 400	0.100
		Concentrated Hydrochloric Acid	0.005

Example 2: Stability of Solutions of Itraconazole upon Dilution in Simulated Gastric Fluid

Carriers were prepared according to Example 1, using the specific carrier formulations shown in Example 1 as Nos. 27-31. From 10 to 85 mg of itraconazole was included in the carriers, as indicated in Table 21. An aliquot of each solution of itraconazole was diluted 100-fold in an enzyme-free simulated gastric fluid (SGF). The diluent was incubated at 37 °C while being tumbled on a rotor. At the indicated time during the incubation, the amount of itraconazole remaining solubilized in the diluent was determined by drug specific HPLC, as a measure of the stability of these formulations in the SGF. A dosage form of a commercial oral itraconazole product, SPORANOX® (a 10 mg/mL drink solution) was also tested under the same experimental conditions, for comparison.

Table 21: Stability of Compositions in SGF

Formulation	Itraconazole (mg/mL)	% Itraconazole Remaining Solubilized in the Diluent After: 1 hr	2 hr	4 hr	6 hr	24 hr
27	30	71.9	69.9	71.5	65.6	
27	85	41.4	45.8	47.3	45.2	6.4
28	30		101.8	96.5	95.4	88.7
28	40		72.2	74.7	79.9	78.9
28	50		54.1	58.8	67.7	48.3
29	30			93.5		94.5
29	50			54.9		64.7
30	10	92.5	95.8	89.3	91.6	78.6
30	20	94.4	89.6	78.0	78.4	66.2
30	30	84.3	78.4	71.0	66.9	69.1
31	10	99.3	94.3	86.5	92.4	78.5
31	30	99.7	98.1	91.7	94.1	87.5
SPORANOX®	10	104.8	104.8	105.0	98.8	94.2

EXAMPLE 3: Stability of Solutions of Itraconazole upon Dilution in Simulated Intestinal Fluid

Carriers were prepared according to Example 1, using the specific carrier formulations shown in Example 1 as Nos. 27-29 and 31. From 10 to 85 mg of itraconazole was included in the carriers, as indicated in Table 22. An aliquot of each solution of itraconazole was diluted 100-fold in an enzyme-free simulated intestinal fluid (SIF). The diluent was incubated at 37 °C while being tumbled on a rotor. At the indicated time during the incubation, the amount of itraconazole remaining solubilized in the diluent was determined by HPLC, as a measure of the stability of these formulations in the SIF. Two dosage forms of a commercial oral itraconazole product, SPORANOX® (a 10 mg/mL drink solution and a 100 mg hard gelatin capsule) were also tested under the same experimental conditions, for comparison.

Table 22: Stability of Compositions in SIF

Formulation	Itraconazole (mg/mL)	% Itraconazole Remaining Solubilized in the Diluent After: 1 hr	2 hr	4 hr	6 hr	24 hr
27	30	90.9	91.1	88.9		60.2
27	85	26.8	15.3	5.5		
28	10	86.1	85.8	81.5		62.6
28	30	81.8	85.8	83.1		3.5
28	40	82.1	83.6	81.9		1.8
29	30	77.6	77.1	71.0		1.7
31	10		29.7	25.2	n.d.	
31	30		30.7	29.3	18.4	
SPORANOX	10	2.2	6.1	4.1		n.d.
SPORANOX	100 mg capsule	n.d.	n.d.	n.d.		

n.d.: not detectable

EXAMPLE 4: Stability of Solutions of Tretinoin upon Dilution in Simulated Gastric Fluid

Example 2 was repeated, but using tretinoin as the ionizable hydrophobic therapeutic agent and formulation Nos. 65 and 66 as the carrier. The results are shown in Table 23.

Table 23: Stability of Compositions in SGF

Formulation	Tretinoin (mg/mL)	% Tretinoin Remaining Solubilized in the Diluent After 3 hr.
65	10	84.5
66	10	49.3

EXAMPLE 5: Stability of Solutions of Tretinoin upon Dilution in Simulated Intestinal Fluid

Example 4 was repeated in simulated intestinal fluid instead of simulated gastric fluid. The results are shown in Table 24.

Table 24: Stability of Compositions in SIF

Formulation	Tretinoin (mg/mL)	% Tretinoin Remaining Solubilized in the Diluent After 3 hr.
65	10	92.5
66	10	53.7

The present invention may be embodied in other specific forms without departing from its spirit or essential characteristics. The described embodiments are to be considered in all respects only as illustrative and not restrictive. The scope of the invention is, therefore, indicated by the appended claims rather than by the foregoing description. All changes which come within the meaning and range of equivalency of the claims are to be embraced within their scope.

What is claimed is:

1. A pharmaceutical composition comprising:

(a) a hydrophobic therapeutic agent having at least one ionizable functional group; and

(b) a carrier, said carrier comprising:

(i) an ionizing agent capable of ionizing the ionizable functional group;

(ii) a surfactant; and

(iii) a triglyceride.

2. The pharmaceutical composition of claim 1, wherein the ionizable functional group is an acidic functional group, and the ionizing agent is a pharmaceutically acceptable base.

3. The pharmaceutical composition of claim 2, wherein the acidic functional group is selected from the group consisting of carboxylic acids, imidazolidinediones, thiazolidinediones, pyrimidinetriones, hydroxyheteroaromatics, phenols, phosphoric acids, sulfuric acids, sulfonic acids, sulfonamides, aminosulfones, sulfonylureas, tetrazoles and thiols.

4. The pharmaceutical composition of claim 2, wherein the hydrophobic therapeutic agent is selected from the group consisting of acetazolamide, acetohexamide, acrivastine, alatrofloxacin, albuterol, alclofenac, aloxiprin, alprostadil, amodiaquine, amphotericin, amylobarbital, aspirin, atorvastatin, atovaquone, baclofen, barbital, benezepril, bezafibrate, bromfenac, bumetanide, butobarbital, candesartan, capsacin, captopril, cefazolin, celecoxib, cephadrine, cephalexin, cerivistatin, cetrizine, chlorambucil, chlorothiazide, chlorpropamide, chlorthalidone, cinoxacin, ciprofloxacin, clinofibrate, cloxacillin, cromoglicate, cromolyn, dantrolene, dichlorophen, diclofenac, dicloxacillin, dicumarol, diflunisal, dimenhydrinate, divalproen, docusate, dronabinol, enoximone, enalapril, enoxacin, enrofloxacin, epalrestate, eposartan, essential fatty acids, estramustine, ethacrynic acid, ethotoin, etodolac, etoposide, fenbufen, fenoprofen, fexofenadine, fluconazole, flurbiprofen, fluvastatin, fosinopril, fosphenytoin, fumagillin, furosemide, gabapentin, gemfibrozil, gliclazide, glipizide, glybenclamide, glyburide, glymepiride, grepafloxacin, ibufenac, ibuprofen, imipenem, indomethacin, irbesartan, isotretinoin, ketoprofen, ketorolac, lamotrigine, levofloxacin, levothyroxine, lisinopril, lomefloxacin, losartan, lovastatin, meclofenamic acid, mefenamic acid, mesalamine, methotrexate, metolazone, montelukast, nalidixic acid, naproxen, natamycin, nimesulide,

nitrofurantoin, non-essential fatty acids, norfloxacin, nystatin, ofloxacin, oxacillin, oxaprozin, oxyphenbutazone, penicillins, pentobarbital, perfloxacin, phenobarbital, phenytoin, pioglitazone, piroxicam, pramipexol, pranlukast, pravastatin, probenecid, probucol, propofol, propylthiouracil, quinapril, rabeprazole, repaglinide, rifampin, rifapentine, sparfloxacin, sulfabenzamide, sulfacetamide, sulfadiazine, sulfadoxine, sulfamerazine, sulfamethoxazole, sulfafurazole, sulfapyridine, sulfasalazine, sulindac, sulphasalazine, sulthiame, telmisartan, teniposide, terbutaline, tetrahydrocannabinol, tirofiban, tolazamide, tolbutamide, tolcapone, tolmetin, tretinoin, troglitazone, trovafloxacin, undecenoic acid, ursodeoxycholic acid, valproic acid, valsartan, vancomycin, verteporfin, vigabatrin, vitamin K-S (II), zafirlukast, and pharmaceutically acceptable salts thereof.

5. The pharmaceutical composition of claim 4, wherein the hydrophobic therapeutic agent is selected from the group consisting of acetohexamide, acrivastine, alatrofloxacin, albuterol, alclofenac, amodiaquine, amphotericin, aspirin, atorvastatin, atovaquone, baclofen, benezepril, bezafibrate, bromfenac, butobarbital, candesartan, capsacin, captopril, celecoxib, cerivistatin, cetrizine, chlorambucil, chlorpropamide, chlorthalidone, clinofibrate, cinoxacin, ciprofloxacin, clinofibrate, cloxacillin, cromoglicate, cromolyn, dantrolene, diclofenac, dicumarol, divalproen, docusate, dronabinol, enalapril, enoxacin, epalrestate, eposartan, etodolac, etoposide, fenbufen, fenoprofen, fexofenadine, fluconazole, flurbiprofen, fluvastatin, fosphenytoin, fumagillin, gabapentin, gemfibrozil, gliclazide, glipizide, glyburide, glymepiride, grepafloxacin, ibufenac, ibuprofen, imipenem, indomethacin, irbesartan, isotretinoin, ketoprofen, ketorolac, lamotrigine, levofloxacin, levothyroxine, lisinopril, lomefloxacin, losartan, lovastatin, mesalamine, methotrexate, montelukast, naproxen, nimesulide, non-essential fatty acids, norfloxacin, ofloxacin, oxaprozin, phenytoin, pioglitazone, piroxicam, pramipexol, pravastatin, probucol, propofol, rabeprazole, repaglinide, rifampin, rifapentine, sparfloxacin, sulfadiazine, sulfamethoxazole, sulfasalazine, sulindac, sulphasalazine, telmisartan, teniposide, terbutaline, tetrahydrocannabinol, tirofiban, tolazamide, tolbutamide, tolcapone, tolmetin, tretinoin, troglitazone, trovafloxacin, undecenoic acid, valproic acid, valsartan, vancomycin, verteporfin, vigabatrin, vitamin K-S (II), zafirlukast, and pharmaceutically acceptable salts thereof.

6. The pharmaceutical composition of claim 5, wherein the hydrophobic therapeutic agent is selected from the group consisting of acrivastine, alatrofloxacin,

albuterol, alclofenac, aspirin, atorvastatin, atovaquone, baclofen, benezepril, bezafibrate, bromfenac, butobarbital, celecoxib, cerivistatin, cetrizine, chlorpropamide, ciprofloxacin, cromoglicate, cromolyn, dantrolene, diclofenac, dicumarol, divalproen, dronabinol, enoxacin, epalrestate, etodolac, etoposide, fenoprofen, fexofenadine, fluconazole, flurbiprofen, fluvastatin, fosphenytoin, gemfibrozil, glipizide, glyburide, glymepiride, grepafloxacin, ibufenac, ibuprofen, isotretinoin, ketoprofen, ketorolac, lamotrigine, levofloxacin, levothyroxine, lomefloxacin, lovastatin, methotrexate, montelukast, naproxen, nimesulide, non-essential fatty acids, norfloxacin, ofloxacin, oxaprozin, phenytoin, pioglitazone, piroxicam, pravastatin, probucol, rabeprazole, repaglinide, rifampin, rifapentine, sulfamethoxazole, sulfasalazine, teniposide, tetrahydrocannabinol, tolcapone, tolmetin, tretinoin, troglitazone, trovafloxacin, valproic acid, vancomycin, vitamin K-S (II), zafirlukast, and pharmaceutically acceptable salts thereof.

7. The pharmaceutical composition of claim 6, wherein the hydrophobic therapeutic agent is selected from the group consisting of alclofenac, aspirin, atorvastatin, atovaquone, benezepril, bromfenac, celecoxib, cromoglicate, cromolyn, diclofenac, dronabinol, epalrestate, etodolac, fexofenadine, flurbiprofen, glymepiride, ibufenac, ibuprofen, isotretinoin, ketorolac, levothyroxine, naproxen, non-essential fatty acids, oxaprozin, phenytoin, pioglitazone, rabeprazole, repaglinide, teniposide, tetrahydrocannabinol, tolmetin, tretinoin, troglitazone, trovafloxacin, vitamin K-S (II), and pharmaceutically acceptable salts thereof.

8. The pharmaceutical composition of claim 2, wherein the base is an amino acid, an amino acid ester, ammonium hydroxide, potassium hydroxide, sodium hydroxide, sodium hydrogen carbonate, aluminum hydroxide, calcium carbonate, magnesium hydroxide, magnesium aluminum silicate, synthetic aluminum silicate, synthetic hydrotalcite, magnesium aluminum hydroxide, diisopropylethylamine, ethanolamine, ethylenediamine, triethanolamine, triethylamine, triisopropanolamine, or a salt of a pharmaceutically acceptable cation and acetic acid, acrylic acid, adipic acid, alginic acid, alkanesulfonic acid, an amino acid, ascorbic acid, benzoic acid, boric acid, butyric acid, carbonic acid, citric acid, a fatty acid, formic acid, fumaric acid, gluconic acid, hydroquinosulfonic acid, isoascorbic acid, lactic acid, maleic acid, methanesulfonic acid, oxalic acid, para-bromophenylsulfonic acid, propionic acid, p-toluenesulfonic acid, salicylic acid, stearic acid, succinic acid, tannic acid, tartaric acid, thioglycolic acid, toluenesulfonic acid, and uric acid, or a mixture thereof.

9. The pharmaceutical composition of claim 1, wherein the ionizable functional group is a basic functional group, and the ionizing agent is a pharmaceutically acceptable acid.

10. The pharmaceutical composition of claim 9, wherein the basic functional group is selected from the group consisting of aliphatic amines, aromatic amines, *C*-substituted aromatic amines, *N*-substituted aromatic amines, heterocyclic amines, *C*-substituted heterocyclic amines and *N*-substituted heterocyclic amines.

11. The pharmaceutical composition of claim 9, wherein the hydrophobic therapeutic agent is selected from the group consisting of abacavir, acebutolol, acrivastine, alatrofloxacin, albuterol, albendazole, alprazolam, alprenolol, amantadine, amiloride, aminoglutethimide, amiodarone, amitriptyline, amlodipine, amodiaquine, amoxapine, amphetamine, amphotericin, amprenavir, amrinone, amsacrine, astemizole, atenolol, atropine, azathioprine, azelastine, azithromycin, baclofen, benethamine, benidipine, benzhexol, benznidazole, benztropine, biperiden, bisacodyl, bisanthrene, bromazepam, bromocriptine, bromperidol, brompheniramine, brotizolam, bupropion, butenafine, butoconazole, cambendazole, camptothecin, carbinoxamine, cephadrine, cephalexin, cetrizine, cinnarizine, chlorambucil, chlopheniramine, chloproguanil, chlordiazepoxide, chlorpromazine, chlorprothixene, chloroquine, cimetidine, ciprofloxacin, cisapride, citalopram, clarithromycin, clemastine, clemizole, clenbuterol, clofazimine, clomiphene, clonazepam, clopidrogel, clozapine, clotiazepam, clotrimazole, codeine, cyclizine, cyproheptadine, dacarbazine, darodipine, decoquinate, delavirdine, demeclocycline, dexamphetamine, dexchlopheniramine, dexfenfluramine, diamorphine, diazepam, diethylpropion, dihydrocodeine, dihydroergotamine, dilitazem, dimenhydrinate, diphenhydramine, diphenooxylate, diphenylimidazole, diphenylpyrallin, dipyridamole, dirithromycin, disopyramide, dolasetron, domperidone, donepezil, doxazosin, doxycycline, droperidol, econazole, efavirenz, ellipticine, enalapril, enoxacin, enrofloxacin, eperisone, ephedrine, ergotamine, erythromycin, ethambutol, ethionamide, ethopropazine, etoperidone, famotidine, felodipine, fenbendazole, fenfluramine, fenoldopam, fentanyl, fexofenadine, flecainide, flucytosine, flunarizine, flunitrazepam, fluopromazine, fluoxetine, flupentixol, flupentixol decanoate, fluphenazine, fluphenazine decanoate, flurazepam, flurithromycin, frovatriptan, gabapentin, granisetron, grepafloxacin, guanabenz, halofantrine, haloperidol, hyoscyamine, imipenem, indinavir, irinotecan, isoxazole, isradipine, itraconazole, ketoconazole, ketotifen, labetalol,

lamivudine, lanosprazole, leflunomide, levofloxacin, lisinopril, lomefloxacin, loperamide, loratadine, lorazepam, lormetazepam, lysuride, mepacrine, maprotiline, mazindol, mebendazole, meclozine, medazepam, mefloquine, melonicam, meptazinol, mercaptopurine, mesalamine, mesoridazine, metformin, methadone, methaqualone, methylphenidate, methylphenobarbital, methysergide, metoclopramide, metoprolol, metronidazole, mianserin, miconazole, midazolam, miglitol, minoxidil, mitomycins, mitoxantrone, molindone, montelukast, morphine, mortriptyline, moxifloxacin, nadolol, nalbuphine, naratriptan, natamycin, nefazodone, nelfinavir, nevirapine, nicardipine, nicotine, nifedipine, nimodipine, nimorazole, nisoldipine, nitrazepam, nitrofurazone, nizatidine, norfloxacin, nystatin, ofloxacin, olanzapine, omeprazole, ondansetron, ornidazole, oxamniquine, oxantel, oxatomide, oxazepam, oxfendazole, oxiconazole, oxprenolol, oxybutynin, oxyphencylcimine, paroxetine, pentazocine, pentoxifylline, perchloperazine, perfloxacin, perphenazine, phenbenzamine, pheniramine, phenoxybenzamine, phentermine, physostigmine, pimozide, pindolol, pizotifen, pramipexol, pranlukast, praziquantel, prazosin, procarbazine, prochlorperazine, proguanil, propranolol, pseudoephedrine, pyrantel, pyrimethamine, quetiapine, quinidine, quinine, raloxifene, ranitidine, remifentanil, repaglinide, reserpine, ricobendazole, rifabutin, rifampin, rifapentine, rimantadine, risperidone, ritonavir, rizatriptan, ropinirole, rosiglitazone, roxaditine, roxithromycin, salbutamol, saquinavir, selegiline, sertraline, sibutramine, sildenafil, sparfloxacin, spiramycins, stavudine, sulconazole, sulphasalazine, sulpiride, sumatriptan, tacrine, tamoxifen, tamsulosin, temazepam, terazosin, terbinafine, terbutaline, terconazole, terfenadine, tetramisole, thiabendazole, thioguanine, thioridazine, tiagabine, ticlopidine, timolol, tinidazole, tioconazole, tirofiban, tizanidine, tolterodine, topotecan, toremifene, tramadol, trazodone, triamterene, triazolam, trifluoperazine, trimethoprim, trimipramine, tromethamine, tropicamide, trovafloxacin, vancomycin, venlafaxine, vigabatrin, vinblastine, vincristine, vinorelbine, vitamin K_5, vitamin K_6, vitamin K_7, zafirlukast, zolmitriptan, zolpidem, zopiclone, and pharmaceutically acceptable salts thereof.

12. The pharmaceutical composition of claim 11, wherein the hydrophobic therapeutic agent is selected from the group consisting of abacavir, acebutolol, acrivastine, alatrofloxacin, albendazole, albuterol, alprazolam, amiodarone, amlodipine, amodiaquine, amphetamine, amphotericin, amprenavir, astemizole, atenolol, azathioprine, azelastine, azithromycin, baclofen, benztropine, bisacodyl, bromazepam,

bromperidol, brompheniramine, bupropion, butenafine, butoconazole, cambendazole, camptothecin, carbinoxamine, cetrizine, cinnarizine, chlopheniramine, chlorambucil, chlorpromazine, cimetidine, ciprofloxacin, cisapride, citalopram, clarithromycin, clemastine, clemizole, clomiphene, clonazepam, clopidrogel, clozapine, clotiazepam, clotrimazole, codeine, cyclizine, delavirdine, dexamphetamine, dexchlopheniramine, diamorphine, diazepam, diethylpropion, dihydrocodeine, dihydroergotamine, dilitazem, diphenhydramine, diphenylimidazole, diphenylpyrallin, dipyridamole, dirithromycin, disopyramide, dolasetron, domperidone, donepezil, doxazosin, droperidol, econazole, efavirenz, ellipticine, enalapril, enoxacin, eperisone, ergotamine, famotidine, felodipine, fenfluramine, fenoldopam, fexofenadine, fentanyl, flecainide, flunarizine, fluopromazine, fluoxetine, frovatriptan, gabapentin, granisetron, halofantrine, imipenem, indinavir, irinotecan, isoxazole, isradipine, itraconazole, ketoconazole, ketotifen, labetalol, lamivudine, lanosprazole, leflunomide, levofloxacin, lisinopril, lomefloxacin, loperamide, loratadine, lorazepam, lormetazepam, mazindol, mebendazole, mefloquine, mercaptopurine, mesalamine, metformin, methadone, methaqualone, methylphenidate, methysergide, metoclopramide, metoprolol, metronidazole, miconazole, midazolam, miglitol, minoxidil, mitoxantrone, montelukast, naratriptan, nelfinavir, nevirapine, nicardipine, nicotine, nifedipine, nimodipine, nimorazole, nisoldipine, nizatidine, norfloxacin, ofloxacin, olanzapine, omeprazole, ondansetron, oxamniquine, oxiconazole, paroxetine, perchloperazine, phenbenzamine, pheniramine, phentermine, physostigmine, pizotifen, pramipexol, prazosin, prochlorperazine, pseudoephedrine, quetiapine, quinidine, raloxifene, ranitidine, remifentanil, repaglinide, rifabutin, rifampin, rifapentine, rimantadine, risperidone, ritonavir, rizatriptan, rosiglitazone, roxaditine, saquinavir, sibutramine, sildenafil, sparfloxacin, stavudine, sulphasalazine, sumatriptan, tacrine, tamoxifen, tamsulosin, terazosin, terbinafine, terbutaline, terconazole, terfenadine, tiagabine, ticlopidine, tinidazole, tioconazole, tirofiban, tizanidine, tolterodine, topotecan, toremifene, tramadol, trazodone, trovafloxacin, vancomycin, venlafaxine, vigabatrin, vinblastine, vincristine, vinorelbine, vitamin K_5, vitamin K_6, vitamin K_7, zafirlukast, zolmitriptan, zolpidem, zopiclone, and pharmaceutically acceptable salts thereof.

13. The pharmaceutical composition of claim 12, wherein the hydrophobic therapeutic agent is selected from the group consisting of abacavir, acrivastine, alatrofloxacin, albuterol, amiodarone, amlodipine, amphetamine, amprenavir, astemizole,

atenolol, azathioprine, azelastine, azithromycin, baclofen, benztropine, bisacodyl, bromazepam, bromperidol, brompheniramine, bupropion, butenafine, butoconazole, cambendazole, camptothecin, carbinoxamine, cetrizine, cinnarizine, chlopheniramine, chlorpromazine, cimetidine, ciprofloxacin, cisapride, clarithromycin, clemastine, clemizole, clonazepam, clopidrogel, clotrimazole, codeine, dexchlopheniramine, dihydrocodeine, dihydroergotamine, diphenhydramine, diphenylimidazole, diphenylpyrallin, dirithromycin, dolasetron, domperidone, doxazosin, econazole, efavirenz, ellipticine, enoxacin, eperisone, ergotamine, famotidine, fenoldopam, fentanyl, fexofenadine, flunarizine, fluoxetine, frovatriptan, granisetron, grepafloxacin, halofantrine, indinavir, irinotecan, isradipine, itraconazole, ketoconazole, ketotifen, lamivudine, lanosprazole, leflunomide, levofloxacin, loperamide, loratadine, metformin, methadone, methylphenidate, methysergide, metronidazole, miconazole, midazolam, miglitol, mitoxantrone, montelukast, naratriptan, nelfinavir, nicotine, nifedipine, nimorazole, nizatidine, norfloxacin, ofloxacin, omeprazole, perchloperazine, phenbenzamine, physostigmine, pizotifen, pseudoephedrine, quetiapine, quinidine, raloxifene, ranitidine, remifentanil, repaglinide, rifabutin, rifampin, rifapentine, rimantadine, ritonavir, rizatriptan, rosiglitazone, roxaditine, saquinavir, sibutramine, sildenafil, stavudine, sumatriptan, tacrine, tamoxifen, tamsulosin, terazosin, terbinafine, tinidazole, tizanidine, tolterodine, topotecan, toremifene, tramadol, trovafloxacin, vancomycin, vinblastine, vincristine, vinorelbine, vitamin K_5, vitamin K_6, vitamin K_7, zafirlukast, zolmitriptan, zolpidem, and pharmaceutically acceptable salts thereof.

14. The pharmaceutical composition of claim 13, wherein the hydrophobic therapeutic agent is selected from the group consisting of amlodipine, astemizole, brompheniramine, bupropion, carbinoxamine, cetrizine, cimetidine, cisapride, clemastine, clemizole, dihydroergotamine, diphenhydramine, diphenylimidazole, diphenylpyrallin, domperidone, eperisone, famotidine, fexofenadine, frovatriptan, granisetron, itraconazole, ketoconazole, ketotifen, lanosprazole, leflunomide, loperamide, loratadine, methysergide, miglitol, montelukast, naratriptan, nizatidine, omeprazole, ondansetron, phenbenzamine, pseudoephedrine, raloxifene, ranitidine, repaglinide, rifabutin, rimantadine, ritonavir, rizatriptan, rosiglitazone, roxaditine, saquinavir, sibutramine, sildenafil, sumatriptan, tamsulosin, terbinafine, tizanidine, tramadol, trovafloxacin, vitamin K_5, vitamin K_6, vitamin K_7, zafirlukast, zolmitriptan, zolpidem, and pharmaceutically acceptable salts thereof.

15. The pharmaceutical composition of claim 9, wherein the acid is a pharmaceutically acceptable inorganic acid.

16. The pharmaceutical composition of claim 15, wherein the inorganic acid is selected from the group consisting of hydrochloric acid, hydrobromic acid, hydriodic acid, sulfuric acid, carbonic acid, nitric acid, boric acid and phosphoric acid.

17. The pharmaceutical composition of claim 9, wherein the acid is a pharmaceutically acceptable organic acid.

18. The pharmaceutical composition of claim 17, wherein the organic acid is selected from the group consisting of acetic acid, acrylic acid, adipic acid, alginic acid, alkanesulfonic acid, an amino acid, ascorbic acid, benzoic acid, boric acid, butyric acid, carbonic acid, citric acid, a fatty acid, formic acid, fumaric acid, gluconic acid, hydroquinosulfonic acid, isoascorbic acid, lactic acid, maleic acid, methanesulfonic acid, oxalic acid, para-bromophenylsulfonic acid, propionic acid, p-toluenesulfonic acid, salicylic acid, stearic acid, succinic acid, tannic acid, tartaric acid, thioglycolic acid, toluenesulfonic acid, uric acid, and mixtures thereof.

19. The pharmaceutical composition of claim 1, wherein the hydrophobic therapeutic agent is present in an amount that is solubilized by the carrier.

20. The pharmaceutical composition of claim 1, wherein the hydrophobic therapeutic agent is present in a first amount that is solubilized by the carrier and a second amount that is suspended but not solubilized in the carrier.

21. The pharmaceutical composition of claim 1, wherein the surfactant is a hydrophilic surfactant or a mixture of hydrophilic surfactants.

22. The pharmaceutical composition of claim 21, wherein the hydrophilic surfactant is a non-ionic hydrophilic surfactant having an HLB value greater than or equal to about 10.

23. The pharmaceutical composition of claim 22, wherein the non-ionic surfactant is selected from the group consisting of alkylglucosides; alkylmaltosides; alkylthioglucosides; lauryl macrogolglycerides; polyoxyethylene alkyl ethers; polyoxyethylene alkylphenols; polyethylene glycol fatty acids esters; polyethylene glycol glycerol fatty acid esters; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene-polyoxypropylene block copolymers; polyglyceryl fatty acid esters; polyoxyethylene glycerides; polyoxyethylene sterols, derivatives, and analogues thereof; polyoxyethylene vegetable oils; polyoxyethylene hydrogenated vegetable oils; reaction

mixtures of polyols and at least one member of the group consisting of fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols; sugar esters, sugar ethers; sucroglycerides; and mixtures thereof.

24. The pharmaceutical composition of claim 22, wherein the non-ionic hydrophilic surfactant is selected from the group consisting of polyoxyethylene alkylethers; polyethylene glycol fatty acids esters; polyethylene glycol glycerol fatty acid esters; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene-polyoxypropylene block copolymers; polyglyceryl fatty acid esters; polyoxyethylene glycerides; polyoxyethylene vegetable oils; polyoxyethylene hydrogenated vegetable oils; reaction mixtures of polyols and at least one member of the group consisting of fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols; and mixtures thereof.

25. The pharmaceutical composition of claim 24, wherein the glyceride is a monoglyceride, diglyceride, triglyceride, or a mixture thereof.

26. The pharmaceutical composition of claim 24, wherein the reaction mixture comprises the transesterification products of a polyol and at least one member of the group consisting of fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols.

27. The pharmaceutical composition of claim 24, wherein the polyol is glycerol, ethylene glycol, polyethylene glycol, sorbitol, propylene glycol, pentaerythritol or a mixture thereof.

28. The pharmaceutical composition of claim 22, wherein the hydrophilic surfactant is PEG-10 laurate, PEG-12 laurate, PEG-20 laurate, PEG-32 laurate, PEG-32 dilaurate, PEG-12 oleate, PEG-15 oleate, PEG-20 oleate, PEG-20 dioleate, PEG-32 oleate, PEG-200 oleate, PEG-400 oleate, PEG-15 stearate, PEG-32 distearate, PEG-40 stearate, PEG-100 stearate, PEG-20 dilaurate, PEG-25 glyceryl trioleate, PEG-32 dioleate, PEG-20 glyceryl laurate, PEG-30 glyceryl laurate, PEG-20 glyceryl stearate, PEG-20 glyceryl oleate, PEG-30 glyceryl oleate, PEG-30 glyceryl laurate, PEG-40 glyceryl laurate, PEG-40 palm kernel oil, PEG-50 hydrogenated castor oil, PEG-40 castor oil, PEG-35 castor oil, PEG-60 castor oil, PEG-40 hydrogenated castor oil, PEG-60 hydrogenated castor oil, PEG-60 corn oil, PEG-6 caprate/caprylate glycerides, PEG-8 caprate/caprylate glycerides, polyglyceryl-10 laurate, PEG-30 cholesterol, PEG-25 phyto sterol, PEG-30 soya sterol, PEG-20 trioleate, PEG-40 sorbitan oleate, PEG-80 sorbitan laurate, polysorbate 20, polysorbate 80, POE-9 lauryl ether, POE-23 lauryl ether, POE-

10 oleyl ether, POE-20 oleyl ether, POE-20 stearyl ether, tocopheryl PEG-100 succinate, PEG-24 cholesterol, polyglyceryl-10 oleate, Tween 40, Tween 60, sucrose monostearate, sucrose monolaurate, sucrose monopalmitate, PEG 10-100 nonyl phenol series, PEG 15-100 octyl phenol series, a poloxamer, or a mixture thereof.

29. The pharmaceutical composition of claim 22, wherein the hydrophilic surfactant is PEG-20 laurate, PEG-20 oleate, PEG-35 castor oil, PEG-40 palm kernel oil, PEG-40 hydrogenated castor oil, PEG-60 corn oil, PEG-25 glyceryl trioleate, polyglyceryl-10 laurate, PEG-6 caprate/caprylate glycerides, PEG-8 caprate/caprylate glycerides, PEG-30 cholesterol, polysorbate 20, polysorbate 80, POE-9 lauryl ether, POE-23 lauryl ether, POE-10 oleyl ether, PEG-24 cholesterol, sucrose monostearate, sucrose monolaurate, a poloxamer, or a mixture thereof.

30. The pharmaceutical composition of claim 22, wherein the hydrophilic surfactant is PEG-35 castor oil, PEG-40 hydrogenated castor oil, PEG-60 corn oil, PEG-25 glyceryl trioleate, PEG-6 caprate/caprylate glycerides, PEG-8 caprate/caprylate glycerides, polysorbate 20, polysorbate 80, tocopheryl PEG-1000 succinate, PEG-24 cholesterol, a poloxamer, or a mixture thereof.

31. The pharmaceutical composition of claim 21, wherein the hydrophilic surfactant is an ionic surfactant.

32. The pharmaceutical composition of claim 31, wherein the ionic surfactant is selected from the group consisting of fatty acid salts, bile salts, phospholipids, phosphoric acid esters, carboxylates, sulfates, sulfonates, and mixtures thereof.

33. The pharmaceutical composition of claim 21, wherein the hydrophilic surfactant is a mixture of at least one ionic surfactant and at least one non-ionic hydrophilic surfactant.

34. The pharmaceutical composition of claim 1, wherein the surfactant is a hydrophobic surfactant or mixture of hydrophobic surfactants having an HLB value of less than about 10.

35. The pharmaceutical composition of claim 34, wherein the hydrophobic surfactant is selected from the group consisting of alcohols; polyoxyethylene alkylethers; polyglyceryl fatty acid esters; fatty acids; glycerol fatty acid esters; acetylated glycerol fatty acid esters; lower alcohol fatty acids esters; polyethylene glycol fatty acids esters; polyethylene glycol glycerol fatty acid esters; polypropylene glycol fatty acid esters; polyoxyethylene glycerides; lactic acid derivatives of mono/diglycerides; propylene

glycol diglycerides; sorbitan fatty acid esters; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene-polyoxypropylene block copolymers; transesterified vegetable oils; sterols; sterol derivatives; sugar esters; sugar ethers; sucroglycerides; polyoxyethylene vegetable oils; polyoxyethylene hydrogenated vegetable oils; reaction mixtures of polyols and at least one member of the group consisting of fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols; and mixtures thereof.

36. The pharmaceutical composition of claim 34, wherein the hydrophobic surfactant is selected from the group consisting of fatty acids; lower alcohol fatty acid esters; polyethylene glycol glycerol fatty acid esters; polypropylene glycol fatty acid esters; polyoxyethylene glycerides; glycerol fatty acid esters; acetylated glycerol fatty acid esters; polyglyceryl fatty acid esters; lactic acid derivatives of mono/diglycerides; sorbitan fatty acid esters; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene-polyoxypropylene block copolymers; polyoxyethylene vegetable oils; polyoxyethylene hydrogenated vegetable oils; reaction mixtures of polyols and at least one member of the group consisting of fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols; and mixtures thereof.

37. The pharmaceutical composition of claim 34, wherein the hydrophobic surfactant is selected from the group consisting of lower alcohol fatty acids esters; polypropylene glycol fatty acid esters; propylene glycol fatty acid esters; glycerol fatty acid esters; polyglyceryl fatty acid esters; acetylated glycerol fatty acid esters; lactic acid derivatives of mono/diglycerides; sorbitan fatty acid esters; polyoxyethylene vegetable oils; and mixtures thereof.

38. The pharmaceutical composition of claim 34, wherein the hydrophobic surfactant is a glycerol fatty acid ester, a polyglyceryl fatty acid ester, an acetylated glycerol fatty acid ester, or a mixture thereof.

39. The pharmaceutical composition of claim 38, wherein the glycerol fatty acid ester is a monoglyceride, diglyceride, or a mixture thereof.

40. The pharmaceutical composition of claim 39, wherein the fatty acid of the glycerol fatty acid ester is a C_6 to C_{20} fatty acid or a mixture thereof.

41. The pharmaceutical composition of claim 34, wherein the hydrophobic surfactant is a reaction mixture of a polyol and at least one member of the group consisting of fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols.

42. The pharmaceutical composition of claim 41, wherein the reaction mixture is a transesterification product of a polyol and at least one member of the group consisting of fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols.

43. The pharmaceutical composition of claim 42, wherein the polyol is polyethylene glycol, sorbitol, propylene glycol, pentaerythritol or a mixture thereof.

44. The pharmaceutical composition of claim 34, wherein the hydrophobic surfactant is selected from the group consisting of myristic acid; oleic acid; lauric acid; stearic acid; palmitic acid; PEG 1-4 stearate; PEG 2-4 oleate; PEG-4 dilaurate; PEG-4 dioleate; PEG-4 distearate; PEG-6 dioleate; PEG-6 distearate; PEG-8 dioleate; PEG 3-16 castor oil; PEG 5-10 hydrogenated castor oil; PEG 6-20 corn oil; PEG 6-20 almond oil; PEG-6 olive oil; PEG-6 peanut oil; PEG-6 palm kernel oil; PEG-6 hydrogenated palm kernel oil; PEG-4 capric/caprylic triglyceride, mono, di, tri, tetra esters of vegetable oil and sorbitol; pentaerythrityl di, tetra stearate, isostearate, oleate, caprylate, or caprate; polyglyceryl 2-4 oleate, stearate, or isostearate; polyglyceryl 4-10 pentaoleate; polyglyceryl-3 dioleate; polyglyceryl-6 dioleate; polyglyceryl-10 trioleate; polyglyceryl-3 distearate; propylene glycol mono- or diesters of a C_6 to C_{20} fatty acid; monoglycerides of a C_6 to C_{20} fatty acid; acetylated monoglycerides of C_6 to C_{20} fatty acid; diglycerides of C_6 to C_{20} fatty acids; lactic acid derivatives of monoglycerides; lactic acid derivatives of diglycerides; cholesterol; phytosterol; PEG 5-20 soya sterol; PEG-6 sorbitan tetra, hexastearate; PEG-6 sorbitan tetraoleate; sorbitan monolaurate; sorbitan monopalmitate; sorbitan mono, trioleate; sorbitan mono, tristearate; sorbitan monoisostearate; sorbitan sesquioleate; sorbitan sesquistearate; PEG 2-5 oleyl ether; POE 2-4 lauryl ether; PEG-2 cetyl ether; PEG-2 stearyl ether; sucrose distearate; sucrose dipalmitate; ethyl oleate; isopropyl myristate; isopropyl palmitate; ethyl linoleate; isopropyl linoleate; poloxamers; and mixtures thereof.

45. The pharmaceutical composition of claim 34, wherein the hydrophobic surfactant is selected from the group consisting of oleic acid; lauric acid; glyceryl monocaprate; glyceryl monocaprylate; glyceryl monolaurate; glyceryl monooleate; glyceryl dicaprate; glyceryl dicaprylate; glyceryl dilaurate; glyceryl dioleate; acetylated monoglycerides; propylene glycol oleate; propylene glycol laurate; polyglyceryl-3 oleate; polyglyceryl-6 dioleate; PEG-6 corn oil; PEG-20 corn oil; PEG-20 almond oil;

sorbitan monooleate; sorbitan monolaurate; POE-4 lauryl ether; POE-3 oleyl ether; ethyl oleate; poloxamers; and mixtures thereof.

46. The pharmaceutical composition of claim 1, wherein the surfactant is a mixture of at least one hydrophilic surfactant and at least one hydrophobic surfactant.

47. The pharmaceutical composition of claim 1, wherein the triglyceride is a pharmaceutically acceptable oil, hydrogenated oil, partially hydrogenated oil, medium chain triglyceride, long chain triglyceride, structured triglyceride, or a mixture thereof.

48. The pharmaceutical composition of claim 1, which further comprises a solubilizer.

49. The pharmaceutical composition of claim 48, wherein the solubilizer is selected from the group consisting of alcohols, polyols, amides, esters, propylene glycol ethers and mixtures thereof.

50. The pharmaceutical composition of claim 49, wherein the alcohol or polyol is selected from the group consisting of ethanol, isopropanol, butanol, benzyl alcohol, ethylene glycol, propylene glycol, butanediols and isomers thereof, glycerol, pentaerythritol, sorbitol, transcutol, mannitol, dimethyl isosorbide, polyethylene glycol, polypropylene glycol, polyvinylalcohol, hydroxypropyl methylcellulose and other cellulose derivatives, maltodextrins, cyclodextrins and cyclodextrin derivatives, and mixtures thereof.

51. The pharmaceutical composition of claim 49, wherein the amide is selected from the group consisting of 2-pyrrolidone, 2-piperidone, ε-caprolactam, *N*-alkylpyrrolidone, *N*-hydroxyalkylpyrrolidone, *N*-alkylpiperidone, *N*-alkylcaprolactam, dimethylacetamide, polyvinylpyrrolidone, and mixtures thereof.

52. The pharmaceutical composition of claim 49, wherein the ester is selected from the group consisting of ethyl propionate, tributylcitrate, acetyl triethylcitrate, acetyl tributyl citrate, triethylcitrate, ethyl oleate, ethyl caprylate, ethyl butyrate, triacetin, propylene glycol monoacetate, propylene glycol diacetate, ε-caprolactone and isomers thereof, δ-valerolactone and isomers thereof, β-butyrolactone and isomers thereof, and mixtures thereof.

53. The pharmaceutical composition of claim 48, wherein the solubilizer is selected from the group consisting of ethanol, isopropanol, butanol, benzyl alcohol, ethylene glycol, propylene glycol, butanediol and isomers thereof, glycerol, pentaerythritol, sorbitol, transcutol, mannitol, dimethyl isosorbide, polyethylene glycol,

polypropylene glycol, polyvinylalcohol, hydroxypropyl methylcellulose and other cellulose derivatives, maltodextrins, cyclodextrins and derivatives thereof, ethyl propionate, tributylcitrate, acetyl triethylcitrate, acetyl tributyl citrate, triethylcitrate, ethyl oleate, ethyl caprylate, ethyl butyrate, triacetin, propylene glycol diacetate, ε-caprolactone and isomers thereof, δ-valerolactone and isomers thereof, β-butyrolactone and isomers thereof, 2-pyrrolidone, 2-piperidone, ε-caprolactam, *N*-methylpyrrolidone, *N*-ethylpyrrolidone, *N*-hydroxyethyl pyrrolidone, *N*-octylpyrrolidone, *N*-laurylpyrrolidone, dimethylacetamide, polyvinylpyrrolidone, glycofurol, methoxy PEG, and mixtures thereof.

54. The pharmaceutical composition of claim 48, wherein the solubilizer is selected from the group consisting of ethanol, isopropanol, benzyl alcohol, ethylene glycol, propylene glycol, 1,3-butanediol, glycerol, pentaerythritol, sorbitol, transcutol, glycofurol, dimethyl isosorbide, polyethylene glycol, polyvinylalcohol, hydroxypropyl methylcellulose, methylcellulose, ethylcellulose, hydroxypropylcyclodextrins, sulfobutyl ether derivatives of cyclodextrins, ethyl propionate, tributylcitrate, triethylcitrate, ethyl oleate, ethyl caprylate, triacetin, β-butyrolactone and isomers thereof, 2-pyrrolidone, *N*-methylpyrrolidone, *N*-ethylpyrrolidone, *N*-hydroxyethylpyrrolidone, *N*-octylpyrrolidone, *N*-laurylpyrrolidone, dimethylacetamide, polyvinylpyrrolidone, and mixtures thereof.

55. The pharmaceutical composition of claim 48, wherein the solubilizer is triacetin, triethylcitrate, ethyl oleate, ethyl caprylate, dimethylacetamide, N-methylpyrrolidone, *N*-hydroxyethylpyrrolidone, polyvinylpyrrolidone, hydroxypropyl methylcellulose, hydroxypropyl cyclodextrins, ethanol, polyethylene glycol 200-600, transcutol, glycofurol, propylene glycol, dimethyl isosorbide, or a mixture thereof.

56. The pharmaceutical composition of claim 48, wherein the solubilizer is triacetin, ethanol, polyethylene glycol 400, glycofurol, propylene glycol or a mixture thereof.

57. The pharmaceutical composition of claim 1, wherein the ionizing agent is present in a pre-reaction amount of greater than about 1.5 mole equivalents per mole of ionizable functional group.

58. The pharmaceutical composition of claim 57, which further comprises a neutralizing agent capable of neutralizing a portion of the ionizing agent.

59. The pharmaceutical composition of claim 58, wherein the ionizable functional group is an acidic functional group, the ionizing agent is a pharmaceutically acceptable base, and the neutralizing agent is a pharmaceutically acceptable acid.

60. The pharmaceutical composition of claim 58, wherein the ionizable functional group is a basic functional group, the ionizing agent is a pharmaceutically acceptable acid, and the neutralizing agent is a pharmaceutically acceptable base.

61. The pharmaceutical composition of claim 58, wherein the neutralizing agent is present in a pre-reaction amount sufficient to neutralize the ionizing agent so that the amount of ionizing agent is less than 1.5 mole equivalents per mole of ionizable functional group, based on the amounts of ionizing agent and ionizable functional groups present before reaction with each other but after reaction of the ionizing agent and the neutralizing agent.

62. The pharmaceutical composition of claim 61, wherein the pre-reaction amount of the neutralizing agent is sufficient to neutralize the ionizing agent so that the amount of ionizing agent is less than about 1.0 mole equivalents per mole of ionizable functional group, based on the amounts of ionizing agent and ionizable functional groups present before reaction with each other but after reaction of the ionizing agent and the neutralizing agent.

63. The pharmaceutical composition of claim 1, wherein the ionizing agent is present in a pre-reaction amount of greater than about 1.0 mole equivalents per mole of ionizable functional group.

64. The pharmaceutical composition of claim 1, wherein the ionizing agent is present in a pre-reaction amount of greater than about 0.1 mole equivalents per mole of ionizable functional group.

65. The pharmaceutical composition of claim 1, wherein the ionizing agent is present in a pre-reaction amount of about 0.1 to about 1.5 mole equivalents per mole of ionizable functional group.

66. The pharmaceutical composition of claim 1, wherein the ionizing agent is present in a pre-reaction amount of about 0.1 to about 1.0 mole equivalents per mole of ionizable functional group.

67. The pharmaceutical composition of claim 1, which further comprises an antioxidant, a preservative, a chelating agent, a viscomodulator, a tonicifier, a flavorant, a colorant, an odorant, an opacifier, a suspending agent, a binder, or a mixture thereof.

68. The pharmaceutical composition of claim 1 in the form of a preconcentrate, a diluted preconcentrate, a semi-solid dispersion, a solid dispersion, or a sprayable solution.

69. A dosage form comprising a capsule filled with the pharmaceutical composition of claim 1.

70. A dosage form comprising a capsule filled with the pharmaceutical composition of claim 61.

71. A dosage form comprising a capsule filled with the pharmaceutical composition of claim 62.

72. A dosage form comprising a solid particulate carrier coated with or formed from the pharmaceutical composition of claim 1.

73. A dosage form comprising the pharmaceutical composition of claim 1 formulated as a solution, a cream, a lotion, an ointment, a suppository, a spray, an aerosol, a paste or a gel.

74. The dosage form of claim 69, wherein the capsule is a hard gelatin capsule, a soft gelatin capsule, a starch capsule or an enteric coated capsule.

75. The pharmaceutical composition of claim 1, which further comprises water or an aqueous solution.

76. A pharmaceutical composition comprising:

(a) a hydrophobic therapeutic agent having at least one ionizable functional group; and

(b) a carrier, said carrier comprising:

(i) an ionizing agent capable of ionizing the ionizable functional group and present in a pre-reaction amount of greater than about 1.5 mole equivalents per mole of ionizable functional group; and

(ii) a surfactant.

77. The pharmaceutical composition of claim 76, which further comprises a neutralizing agent capable of neutralizing a portion of the ionizing agent.

78. The pharmaceutical composition of claim 77, wherein the ionizable functional group is an acidic functional group, the ionizing agent is a pharmaceutically acceptable base, and the neutralizing agent is a pharmaceutically acceptable acid.

79. The pharmaceutical composition of claim 77, wherein the ionizable functional group is a basic functional group, the ionizing agent is a pharmaceutically acceptable acid, and the neutralizing agent is a pharmaceutically acceptable base.

80. The pharmaceutical composition of claim 77, wherein the neutralizing agent is present in a pre-reaction amount sufficient to neutralize the ionizing agent so that the amount of ionizing agent is less than 1.5 mole equivalents per mole of ionizable functional group, based on the amounts of ionizing agent and ionizable functional groups present before reaction with each other but after reaction of the ionizing agent and the neutralizing agent.

81. The pharmaceutical composition of claim 80, wherein the pre-reaction amount of the neutralizing agent is sufficient to neutralize the ionizing agent so that the amount of ionizing agent is less than about 1.0 mole equivalents per mole of ionizable functional group, based on the amounts of ionizing agent and ionizable functional groups present before reaction with each other but after reaction of the ionizing agent and the neutralizing agent.

82. A dosage form comprising a capsule filled with the pharmaceutical composition of claim 80.

83. A dosage form comprising a capsule filled with the pharmaceutical composition of claim 81.

84. The dosage form of claim 82, wherein the capsule is a hard gelatin capsule, a soft gelatin capsule, a starch capsule or an enteric coated capsule.

85. The pharmaceutical composition of claim 76, which further comprises water or an aqueous solution.

86. The pharmaceutical composition of claim 76, which further comprises a solubilizer.

87. A pharmaceutical composition comprising:

(a) a hydrophobic therapeutic agent having at least one ionizable functional group; and

(b) a carrier, said carrier comprising:

(i) an ionizing agent capable of ionizing the ionizable functional group;

(ii) a surfactant selected from the group consisting of alkylglucosides; alkylmaltosides; alkylthioglucosides;

lauryl macrogolglycerides; polyoxyethylene alkyl ethers; fatty acids; lower alcohol fatty acid esters; polyoxyethylene alkylphenols; polyethylene glycol fatty acids esters; polypropylene glycol fatty acid esters; glycerol fatty acid esters; acetylated glycerol fatty acid esters; polyethylene glycol glycerol fatty acid esters; polyglyceryl fatty acid esters; polyoxyethylene glycerides; polyoxyethylene sterols, derivatives, and analogues thereof; polyoxyethylene vegetable oils; polyoxyethylene hydrogenated vegetable oils; reaction mixtures of polyols and at least one member of the group consisting of fatty acids, vegetable oils, hydrogenated vegetable oils, and sterols; sugar esters; sugar ethers; sucroglycerides; fatty acid salts; bile salts; phospholipids; phosphoric acid esters; carboxylates; sulfates; and sulfonates; and

(iii) a solubilizer present in an amount of greater than about 10% by weight, based on the total weight of the composition.

88. The pharmaceutical composition of claim 87, wherein the solubilizer is selected from the group consisting of alcohols, polyols, amides, esters, propylene glycol ethers and mixtures thereof.

89. The pharmaceutical composition of claim 87, wherein the solubilizer is selected from the group consisting of ethanol, isopropanol, butanol, benzyl alcohol, ethylene glycol, propylene glycol, butanediol and isomers thereof, glycerol, pentaerythritol, sorbitol, mannitol, dimethyl isosorbide, polyethylene glycol, polypropylene glycol, polyvinylalcohol, hydroxypropyl methylcellulose and other cellulose derivatives, cyclodextrins, clodextrins and derivatives thereof, ethyl propionate, tributylcitrate, acetyl triethylcitrate, acetyl tributyl citrate, triethylcitrate, ethyl oleate, ethyl caprylate, ethyl butyrate, triacetin, propylene glycol diacetate, ε-caprolactone and isomers thereof, δ-valerolactone and isomers thereof, β-butyrolactone and isomers thereof, 2-pyrrolidone, 2-piperidone, ε-caprolactam, *N*-methylpyrrolidone, *N*-ethylpyrrolidone, *N*-hydroxyethyl pyrrolidone, *N*-octylpyrrolidone, *N*-laurylpyrrolidone,

dimethylacetamide, polyvinylpyrrolidone, glycofurol, methoxy PEG, and mixtures thereof.

90. The pharmaceutical composition of claim 87, wherein the solubilizer is present in an amount of at least about 15% by weight, based on the total weight of the composition.

91. The pharmaceutical composition of claim 87, wherein the ionizing agent is present in a pre-reaction amount of greater than about 1.5 mole equivalents per mole of ionizable functional group.

92. The pharmaceutical composition of claim 87, wherein the ionizing agent is present in a pre-reaction amount of greater than about 1.0 mole equivalents per mole of ionizable functional group.

93. The pharmaceutical composition of claim 87, wherein the ionizing agent is present in a pre-reaction amount of greater than about 0.1 mole equivalents per mole of ionizable functional group.

94. The pharmaceutical composition of claim 87, wherein the ionizing agent is present in a pre-reaction amount of about 0.1 to about 1.5 mole equivalents per mole of ionizable functional group.

95. The pharmaceutical composition of claim 87, wherein the ionizing agent is present in a pre-reaction amount of about 0.1 to about 1.0 mole equivalents per mole of ionizable functional group.

96. A dosage form comprising a capsule filled with the pharmaceutical composition of claim 94.

97. A dosage form comprising a capsule filled with the pharmaceutical composition of claim 95.

98. A pharmaceutical composition comprising:

(a) a hydrophobic therapeutic agent having at least one ionizable functional group; and

(b) a carrier, said carrier comprising:

(i) an ionizing agent capable of ionizing the ionizable functional group;

(ii) a surfactant selected from the group consisting of alkylglucosides; alkylmaltosides; alkylthioglucosides;

lauryl macrogolglycerides; fatty acids; lower alcohol fatty acid esters; polyoxyethylene alkylphenols; polyethylene glycol fatty acids esters; polypropylene glycol fatty acid esters; glycerol fatty acid esters; acetylated glycerol fatty acid esters; polyethylene glycol glycerol fatty acid esters; polyglyceryl fatty acid esters; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene glycerides; polyoxyethylene sterols, derivatives, and analogues thereof; polyoxyethylene vegetable oils; polyoxyethylene hydrogenated vegetable oils; reaction mixtures of polyols and at least one member of the group consisting of fatty acids, vegetable oils, hydrogenated vegetable oils, and sterols; sugar esters; sugar ethers; sucroglycerides; fatty acid salts; bile salts; phospholipids; phosphoric acid esters; carboxylates; sulfates; and sulfonates; and

(iii) a solubilizer comprising at least one compound selected from the group consisting of alcohols, polyols, amides, esters, and propylene glycol ethers, the alcohol or polyol being selected from the group consisting of ethanol, isopropanol, butanol, benzyl alcohol, ethylene glycol, propylene glycol, butanediols and isomers thereof, glycerol, pentaerythritol, sorbitol, mannitol, dimethyl isosorbide, polypropylene glycol, polyvinylalcohol, hydroxypropyl methylcellulose and other cellulose derivatives, maltodextrins, and cyclodextrins and cyclodextrin derivatives.

99. The pharmaceutical composition of claim 98, wherein the ionizing agent is present in a pre-reaction amount of greater than about 1.5 mole equivalents per mole of ionizable functional group.

100. The pharmaceutical composition of claim 98, wherein the ionizing agent is present in a pre-reaction amount of greater than about 1.0 mole equivalents per mole of ionizable functional group.

101. The pharmaceutical composition of claim 98, wherein the ionizing agent is present in a pre-reaction amount of greater than about 0.1 mole equivalents per mole of ionizable functional group.

102. The pharmaceutical composition of claim 98, wherein the ionizing agent is present in a pre-reaction amount of about 0.1 to about 1.5 mole equivalents per mole of ionizable functional group.

103. The pharmaceutical composition of claim 98, wherein the ionizing agent is present in a pre-reaction amount of about 0.1 to about 1.0 mole equivalents per mole of ionizable functional group.

104. A dosage form comprising a capsule filled with the pharmaceutical composition of claim 102.

105. A dosage form comprising a capsule filled with the pharmaceutical composition of claim 103.

106. A method of preparing a pharmaceutical composition of an ionizable hydrophobic therapeutic agent, the method comprising

(I) providing a pharmaceutical composition comprising:

(a) a hydrophobic therapeutic agent having at least one ionizable functional group; and

(b) a carrier, the carrier comprising:

(i) an ionizing agent capable of ionizing the ionizable functional group; and

(ii) a surfactant; and

(II) providing a neutralizing agent in an amount sufficient to neutralize at least a portion of the ionizing agent.

107. The method of claim 106, wherein the ionizing agent is present in the carrier in a pre-reaction amount of greater than about 1.5 mole equivalents per mole of ionizable functional group.

108. The method of claim 106, wherein the neutralizing agent is present in a pre-reaction amount sufficient to neutralize the ionizing agent so that the amount of ionizing agent is less than 1.5 mole equivalents per mole of ionizable functional group, based on the amounts of ionizing agent and ionizable functional groups present before

reaction with each other but after reaction of the ionizing agent and the neutralizing agent.

109. The method of claim 107, wherein the pre-reaction amount of the neutralizing agent is sufficient to neutralize the ionizing agent so that the amount of ionizing agent is less than about 1.0 mole equivalents per mole of ionizable functional group, based on the amounts of ionizing agent and ionizable functional groups present before reaction with each other but after reaction of the ionizing agent and the neutralizing agent.

110. A method of treating an animal with an ionizable hydrophobic therapeutic agent, the method comprising:

(I) providing a dosage form of a pharmaceutical composition comprising:

(a) a hydrophobic therapeutic agent having at least one ionizable functional group; and

(b) a carrier, said carrier comprising:

(i) an ionizing agent capable of ionizing the ionizable functional group; and

(ii) a surfactant; and

(II) administering said dosage form to said animal.

111. The method of claim 110, wherein the pharmaceutical composition further comprises a triglyceride.

112. The method of claim 110, wherein the dosage form is a capsule, a solution, a cream, a lotion, an ointment, a suppository, a spray, an aerosol, a paste or a gel.

113. The method of claim 110, wherein the dosage form is administered by an oral, parenteral, topical, transdermal, ocular, pulmonary, vaginal, rectal or transmucosal route.

114. The method of claim 110, wherein the animal is a mammal.

115. The method of claim 114, wherein the mammal is a human.

INTERNATIONAL SEARCH REPORT

In. ational application No.
PCT/US00/07342

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) :A61K 9/14, 9/48, 9/64, 9/66; A01N 25/00
US CL :424/ 451, 455, 456, 489; 514/785
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/ 451, 455, 456, 489; 514/785

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

West

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,342,625 A (HAUER et al.) 30 August 1994, see column 1, lines 11-20, column 7, lines 55-60, column 8, lines 65 through column 11, lines 1-56, column 16, lines 8-14, column 20, lines 42-46.	1-21, 23-26, 31-33, 67, 69-71, 75, 110-113
Y	US 4,944,949 A (STORY et al.) 31 July 1990, see column 3, lines 23-44, column 4, lines 39-66, column 7, lines 26-35, column 8, lines 3-37.	1-47, 69-71, 110, 112, 113
A	US 4,306,981 A (BLAIR, Jr.) 22 December 1981, see column 8, lines 31-46, column 9, lines 15-68.	48-67, 76-85, 87-95, 97-103, 106-109

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"B"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 28 JUNE 2000	Date of mailing of the international search report 23 AUG 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer SUSAN TRAN Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet) (July 1998)*

INTERNATIONAL SEARCH REPORT

Int...ational application No.
PCT/US00/07342

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
1-67, 75-95, 98-103, 106-113

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☒ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet(1)) (July 1998)★

INTERNATIONAL SEARCH REPORT

Int .ational application No.
PCT/US00/07342

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claim(s) 1-67, 87-95, 98-103, 106-109, and 111, drawn to pharmaceutical composition.
Group II, claim(s) 68-75, drawn to form of the composition.
Group III, claim(s) 1-67, 69-71, 74, 96-97, 104, 105, drawn to capsule.
Group IV, claim(s) 1-67, and 72, drawn to coated particle.
Group V, claim(s) 1-67, and 73, drawn to suppository.
Group VI, claim(s) 1-67, and 73, drawn to spray, aerosol.
Group VII, claim(s) 1-67, and 73, drawn to solid, paste or gel.
Group VIII, claim(s) 1-67, and 74, drawn to coated capsule.
Group IX, claim(s) 76-84 and 110-113, drawn to composition of invention I without a triglyceride and capsule.
Group X, claim(s) 75-84, drawn to coated capsule.
Group XI, claim(s) 75-86, drawn to aqueous solution.
Group XII, claim(s) 110-112, 114, and 115, drawn to method of treating solution, cream, lotion, ointment.
Group XIII, claim(s) 110, 112, 114, and 115, drawn to supposition.
Group XIV, claim(s) 110, 112, 114, and 115, drawn to spray and aerosol.
Group XV, claim(s) 110, 112, 114, and 115, drawn to solid, paste or gel.
Group XVI, claim(s) 110, and 113-115, drawn to parental.
Group XVII, claim(s) 110, and 113-115, drawn to topical, transdermal.
Group XVIII, claim(s) 110, and 113-115, drawn to ocular.
Group XIX, claim(s) 110, and 113-115, drawn to pulmonary.
Group XX, claim(s) 110, and 113-115, drawn to vaginal.
Group XXI, claim(s) 110, and 113-115, drawn to rectal.

The inventions listed as Groups I to XXI do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:
The invention of groups I-VIII require triglycerin but the invention of groups IX-XXI do not required triglycerin.
The invention of groups II-XIII comprise different products
The invention of groups XII-XXI comprise different process of treating.